



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460**

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**OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES**

**OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361**

MEMORANDUM

Date: November 3, 2009

SUBJECT: Oxamyl: A 2009 benchmark dose (BMD) analysis based on modeling revisions for the comparative sensitivity cholinesterase study (MRID 46615301)

PC Code: 103801

DP Barcode: D371112

MRID No.: 46615301 (no associated DER)

Registration No.: 352-400

Petition No.: NA

Regulatory Action: NA

Risk Assessment Type: NA

Case No.: NA

TXR No.: 0055282

CAS No.: 23135-22-0

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I. CONCLUSIONS

This memo serves to update the benchmark dose (BMD) analysis that was performed for oxamyl in 2008 (TXR 0055220). The 2009 BMD analysis modified how the control values for the brain ChE data from the CCA study were modeled based on comments provided by Exponent (submitted by DuPont; MRID 47386001). The 2009 BMD revisions were performed by Philip Villanueva with the help of Dr. Woodrow Setzer. This 2009 BMD analysis is in support of both the N-methyl carbamate (NMC) cumulative risk assessment (CRA) and the single chemical assessment for oxamyl. This BMD analysis supersedes previous BMD analyses for oxamyl. The 2009 BMD results are provided in the tables below.

*Review in REC
11/10/2009
an*

II. BACKGROUND

Oxamyl is part of the *N*-methyl carbamate (NMC) cumulative risk assessment (CRA). As such, an updated BMD₁₀ and BMDL₁₀ estimate for both adult RBC and brain from the combined AChE data set from all available oxamyl studies is needed for the NMC CRA. In addition, the AChE data specifically obtained from the CCA study will be used to derive the BMD₁₀ and BMDL₁₀ estimates for adult and PND11 pups for the FQPA factor. The 2009 BMD analysis also supports the acute population adjusted dose (aPAD) for the oxamyl single chemical assessment. The 2009 BMD analysis for oxamyl was revised by Philip Villanueva (Health Effects Division) with the help of Dr. Woodrow Setzer (Office of Research and Development).

III. RESULTS/DISCUSSION

Benchmark Dose Analysis

1. Combined Adult Data

The 2009 BMD analysis did not differ from the 2008 BMD analysis for the combined adult data. Detailed results of the 2009 BMD analysis (summary outputs) are included in Appendix A (brain AChE) and Appendix B (RBC AChE). The BMD₁₀ and BMDL₁₀ estimates as well as the recovery half life estimates for the combined adult AChE data are summarized in Table 1 below.

Table 1. 2009 BMD and recovery half-life results for the combined adult oxamyl AChE data¹

| Compartment | BMD ₁₀ | BMDL ₁₀ |
|---|-------------------|-----------------------|
| Adult Brain | 0.184 | 0.155 |
| Adult RBC | 0.154 | 0.090 |
| Adult Brain Half-life Central Estimate & CI | 0.61 hrs | CI 0.55 – 0.69 hrs |
| Adult RBC Half-life Central Estimate & CI | 0.76 hrs | CI 0.65 – 0.88 hrs |

¹Studies included in the 2009 BMD analysis include: MRIDs 44254401, 44472001, 46615301, Padilla (NHEERL). CI: Confidence Interval consisting of the lower and upper bound estimates around the central estimate.

2. CCA Study Results

The 2009 BMD analysis took into consideration modeling suggestions by Exponent. Specifically, Exponent suggested that the missing control groups at the three time points (1.5, 3 and 6 hour time points) be modeled separately rather than fitting a single, common value to all three control value time points, as was previously done by EPA.

Dr. Woodrow Setzer of ORD evaluated how the controls were handled in the EPA modeling of the CCA study. The PND11 data from the CCA study have control groups for the 0.5, 1, 2, and 4 hour time points, but not the 1.5, 3, and 6 hour time points. Evaluation of the control data from the CCA study suggested that the data were heterogeneous (*i.e.*, different from one another over

time) with an upward trend over time. When previously modeling these data (Appendix A), the EPA fit a common control value based on concerns about the precision of modeling separate estimates for the missing control data. Exponent, however, modeled a separate control value for each of the missing time points, which seems to provide a reasonable fit and control estimates that are more realistic than those from the previous EPA analysis. After duplicating Exponent's modeling of the CCA control data (Appendix C), EPA finds Exponent's approach to modeling the control data to be preferred over EPA's previous approach of modeling a common control value for the missing data. For further information please refer to the 2009 response to comment document (Reaves 2009, TXR 0055219).

The BMD estimates and associated FQPA factor based on the EPA's updated BMD analysis, which modifies the modeling of the control data for PND11 brain data from CCA study, are reflected in Table 2 below. Specifically, the PND11 BMD and BMDL differ from the 2008 analysis. The revised BMD for the PND11 brain also changes the FQPA factor from 3.47 (Appendix A) to 2.64 (Appendix C). The RBC ChE data do not differ from the 2008 BMD analysis.

Table 2. 2009 BMD results from the oxamyl CCA study for derivation of the FQPA factor¹

| Compartment | BMD ₁₀ | BMDL ₁₀ | FQPA Factor |
|--|-------------------|--------------------|-----------------------|
| Adult CCA Brain | 0.177 | 0.145 | 2.64 (0.177/0.067) |
| PND11 Brain | 0.067 | 0.043 | |
| Adult CCA RBC | 0.079 | 0.052 | 1.34 (0.079/0.059) |
| PND11 RBC | 0.059 | 0.039 | |
| PND11 Brain Half-Life Central Estimate & CI | 1.34 hrs | | (0.47-3.79 hrs) |
| PND11 RBC Half-Life Central Estimate & CI | 2.54 hrs | | (1.04-6.20 hrs) |

¹Ratio of adult BMD₁₀ to PND11 BMD₁₀ specifically from the oxamyl CCA study MRID 46615301
CI: Confidence Interval consisting of the lower and upper bound estimates around the central estimate.

APPENDIX A

Oxamyl: AChE Rat Brain Summary

Dose-Time Response Modeling of Rat Brain AChE Activity: Oxamyl Gavage Dosing

September 30, 2009

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1 Preamble

Here is some code to set up the analysis: loading required libraries and datasets, and defining some functions.

First, `CarbamateData` loads the full dataset for this risk assessment, and causes the library `DRUtils` to be loaded.

```
> library(CarbamateData)
```

Set up lattice to use B&W instead of color:

```
> library(lattice)
> ltheme <- canonical.theme(color = FALSE)
> ltheme$strip.background$col <- "transparent"
> lattice.options(default.theme = ltheme)
```

Use package `Hmisc` for some formatting support.

```
> library(Hmisc)
```

The rat gavage data for this analysis are in `AggData`, `PadillaData`, and `newdata`. The following code prints out documentation for the datasets in use:

```
> printDataDoc(AggData)
```

```
-----  
Data set: AggData
```

```
Dataset creation date: Mon May 05 12:20:50 2008  
Script name: C:/EmpiricalDoseResponses/Data/getdata.R  
Script last modified: 2008-05-05 12:18:40  
sysname: Windows  
release: XP  
version: build 2600, Service Pack 2  
nodename: L2032JPVILLANU  
machine: x86  
login: pvillanu  
user: pvillanu
```

```
> printDataDoc(PadillaData)
```

```
Data set: PadillaData
```

```
Dataset creation date: Mon May 05 12:20:58 2008  
Script name: C:/EmpiricalDoseResponses/Data/getdata.R  
Script last modified: 2008-05-05 12:18:40  
sysname: Windows  
release: XP  
version: build 2600, Service Pack 2  
nodename: L2032JPVILLANU  
machine: x86  
login: pvillanu  
user: pvillanu
```

```
> printDataDoc(newdata)
```

```
Data set: newdata
```

```
Dataset creation date: Mon May 05 12:20:58 2008  
Script name: C:/EmpiricalDoseResponses/Data/getdata.R  
Script last modified: 2008-05-05 12:18:40  
sysname: Windows  
release: XP  
version: build 2600, Service Pack 2  
nodename: L2032JPVILLANU  
machine: x86  
login: pvillanu  
user: pvillanu
```

The following function turns out to be quite useful on subsetted dataframes. It just eliminates unused levels of all factors in the data frame:

```
> CleanUp <- function(x) {  
+   for (nm in names(x)) {  
+     if (is.factor(x[, nm]))
```

```

+           x[, nm] <- factor(x[, nm])
+
+       }
+
+   x
+
}

```

To get starting values, we often have to extract values from a previously fit model. The following function simplifies that. The argument what is a regular expression:

```

> getParams <- function(what, Par) {
+   Par[grep(what, names(Par))]
+ }

```

This script is for modeling the dose-time response for rat brain via gavage dosing. It includes acute, subchronic, and chronic studies.

All the data used for this DR model are in AggData and in PadillaData. The oxamyl data need to be extracted from both data sets, then several variables ($n = 1$, $sd = 0$, $tmonstdy = 1$, $mrid = "Padilla"$, $cheact = Brain.R$) added to the Padilla dataset. To keep the response scale similar across studies, Padilla's values for cheact need to be divided by 500. Finally the two datasets are combined, and all activity levels and their standard deviation rescaled by ten (this seems to make it easier).

These are all the names used for the brain sections we want from AggData:

```
> BrainSections <- levels(AggData$sctn)[grep("(^BRAIN)|(^WHOLEBRAIN)|(LEFT HEMISPHERE)|(HALFBRAIN)", le
```

Now, set up the analysis dataset.

```

> dta <- CleanUp(subset(AggData, chemical %in% "OXAMYL" & species %in% "RAT" & dsmtd %in% "GAVAGE" & sc
+   !is.na(cheact) & (n == 1 | !is.na(sd)), select = c("cheact", "sd", "n", "dose", "tmpstds", "sex",
> tdt <- with(dta, PhonyDF(dose, n, cheact, sd, "dose", "cheact", Avals = dta[, c("tmpstds", "sex", "m
> tdt$age <- factor(rep("adult", nrow(tdt)), levels = c("adult", "pnd11"))
> tdt$type <- factor(c(`44254401` = "doseresponse", `44420301` = "doseresponse", `44472001` = "timecou
> Pdta <- CleanUp(subset(PadillaData, chemical %in% "oxamyl", select = c("dose", "brain.R", "TMPSTDS"))
> names(Pdta) <- c("dose", "cheact", "tmpstds")
> Pdta$sex <- factor(rep("M", nrow(Pdta)), levels = c("F", "M"))
> Pdta$age <- factor(rep("adult", nrow(Pdta)), levels = c("adult", "pnd11"))
> Pdta$mrid <- factor(rep("padilla", nrow(Pdta)))
> Pdta$cheact <- Pdta$cheact/500
> Pdta$type <- factor(ifelse(abs(Pdta$tmpstds - 2/3) < 0.001, "doseresponse", "timecourse"))
> dta2 <- CleanUp(subset(newdata, chemical %in% "Oxamyl", select = c("dose", "brain", "time", "age", "s
> names(dta2) <- c("dose", "cheact", "tmpstds", "age", "sex", "mrid")
> dta2$tmpstds <- dta2$tmpstds/60
> dta2$age <- factor(ifelse(dta2$age > 40, "adult", "pnd11"))
> dta2$type <- factor(c(rep("timecourse", 100), rep("doseresponse", nrow(dta2) - 100)))
> dta2 <- dta2[!is.na(dta2$cheact), ]
> dta <- rbind(tdt, Pdta[, names(tdt)], dta2[, names(dta2)])

```

Summary of the relevant variables in this dataset:

```
> by(dta, dta$mrid, summary)
```

| dta\$mrid: 44254401 | dose | cheact | tmpstds | sex | mrid | age | type |
|---------------------|---------|----------------|---------------|-------|--------------|-----------|------------------|
| Min. | :0.0000 | Min. : 2.946 | Min. : 1.0 | F:120 | 44254401:239 | adult:239 | doseresponse:239 |
| 1st Qu. | :0.0500 | 1st Qu.:10.436 | 1st Qu.: 1.0 | M:119 | 44472001: 0 | pnd11: 0 | timecourse : 0 |
| Median | :0.1000 | Median :11.326 | Median : 24.0 | | padilla : 0 | | |
| Mean | :0.6757 | Mean :10.473 | Mean :128.8 | | 46615301: 0 | | |
| 3rd Qu. | :1.0000 | 3rd Qu.:12.037 | 3rd Qu.:360.0 | | | | |
| Max. | :2.0000 | Max. :14.131 | Max. :360.0 | | | | |

dta\$mrid: 44472001

| dose | cheact | tmpstds | sex | mrid | age | type |
|-------------|----------------|---------------|------|--------------|-----------|-----------------|
| Min. :0.0 | Min. : 5.035 | Min. : 0.500 | F:80 | 44254401: 0 | adult:160 | doseresponse: 0 |
| 1st Qu.:0.0 | 1st Qu.:11.063 | 1st Qu.:1.625 | M:80 | 44472001:160 | pnd11: 0 | timecourse :160 |
| Median :0.5 | Median :11.727 | Median :2.500 | | padilla : 0 | | |
| Mean :0.5 | Mean :11.146 | Mean : 2.375 | | 46615301: 0 | | |
| 3rd Qu.:1.0 | 3rd Qu.:12.319 | 3rd Qu.:3.250 | | | | |
| Max. :1.0 | Max. :13.908 | Max. :4.000 | | | | |

dta\$mrid: padilla

| dose | cheact | tmpstds | sex | mrid | age | type |
|----------------|----------------|-----------------|------|-------------|----------|-----------------|
| Min. :0.0000 | Min. : 3.879 | Min. : 0.5000 | F: 0 | 44254401: 0 | adult:59 | doseresponse:30 |
| 1st Qu.:0.0833 | 1st Qu.: 7.307 | 1st Qu.: 0.6667 | M:59 | 44472001: 0 | pnd11: 0 | timecourse :29 |
| Median :1.0000 | Median :10.142 | Median : 0.6667 | | padilla :59 | | |
| Mean :0.6751 | Mean : 9.660 | Mean : 3.0847 | | 46615301: 0 | | |
| 3rd Qu.:1.0000 | 3rd Qu.:12.363 | 3rd Qu.: 1.5000 | | | | |
| Max. :1.5000 | Max. :14.670 | Max. :24.0000 | | | | |

dta\$mrid: 46615301

| dose | cheact | tmpstds | sex | mrid | age | type |
|----------------|----------------|----------------|-------|--------------|-----------|------------------|
| Min. :0.0000 | Min. : 3.400 | Min. : 0.500 | F:180 | 44254401: 0 | adult:157 | doseresponse:257 |
| 1st Qu.:0.0750 | 1st Qu.: 5.400 | 1st Qu.: 0.500 | M:175 | 44472001: 0 | pnd11:198 | timecourse : 98 |
| Median :0.1000 | Median : 6.600 | Median : 0.500 | | padilla : 0 | | |
| Mean :0.1121 | Mean : 7.213 | Mean : 1.818 | | 46615301:355 | | |
| 3rd Qu.:0.1500 | 3rd Qu.: 9.400 | 3rd Qu.:4.000 | | | | |
| Max. :0.2500 | Max. :11.700 | Max. :6.000 | | | | |

> with(dta, print(table(dose, tmpstds, interaction(mrid, age, sex, drop = TRUE, sep = ":")), zero.print
, , = 44254401:adult:F

tmpstds

| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
|--------|-----|--------------------|----|-----|---|---|---|---|----|-----|
| 0 | . | . | . | 10 | . | . | . | . | 10 | 10 |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |
| 0.1 | . | . | 10 | . | . | . | . | . | 10 | 10 |
| 0.125 | . | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | 10 | . | . | . | . | . | 10 | 10 |
| 1 | . | . | . | . | . | . | . | . | . | . |
| 1.5 | . | 10 | . | . | . | . | . | . | 10 | 10 |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = 44472001:adult:F

tmpstds

| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
|--------|-----|--------------------|---|-----|----|----|----|---|----|-----|
| 0 | 10 | . | . | . | 10 | 10 | 10 | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |

| | | | | | | | | | |
|-------|----|---|---|----|----|----|---|---|---|
| 0.1 | . | . | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . |
| 1 | 10 | . | . | 10 | 10 | 10 | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . |

, , = 46615301:adult:F

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|----|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |
| 0.1 | . | . | . | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . | . |
| 0.15 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.2 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.25 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | . | . | . | . | . | . | . | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = 46615301:pnd11:F

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|---|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | 5 | 5 | 5 | 5 | 5 | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | 10 | . | . | . | . | . | . | . | . | . |
| 0.1 | 15 | . | 5 | 5 | 5 | 5 | 5 | 5 | . | . |
| 0.125 | 10 | . | . | . | . | . | . | . | . | . |
| 0.15 | 10 | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | . | . | . | . | . | . | . | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = 44254401:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|----|-----|---|---|---|----|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | . | . | 10 | . | . | . | . | 10 | 10 | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |

| | | | | | | | | | |
|-------|---|---|----|---|---|---|---|----|----|
| 0.1 | . | . | 10 | . | . | . | . | 10 | 10 |
| 0.125 | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . |
| 1 | . | . | 10 | . | . | . | . | 10 | 10 |
| 1.5 | . | . | . | . | . | . | . | . | . |
| 2 | . | . | 10 | . | . | . | . | 9 | 10 |

, , = 44472001:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|----|----|----|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | . | . | 10 | 10 | 10 | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |
| 0.1 | . | . | . | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | 10 | . | . | . | 10 | 10 | 10 | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = padilla:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|---|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 1 | . | 5 | 1 | 1 | . | . | 1 | . | 1 |
| 0.0666 | . | . | 5 | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |
| 0.1 | . | . | 5 | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | 5 | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | 5 | . | 5 | 5 | . | . | 5 | . | 4 | . |
| 1.5 | . | . | 5 | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = 46615301:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|---|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | . | . | . | . | 7 | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |

```

0.1      .
0.125     .
0.15    10   .
0.2     10   .
0.25    10   .
0.5      .
0.75      .
1        .
1.5      .
2        .

, , = 46615301:pnd11:M

      tmpstds
dose    0.5 0.6666666666666667  1 1.5  2  3  4  6 24 360
  0     10   . 5   . 5   . 5   .  .  .  .
  0.0666  .   .  .  .  .  .  .  .  .
  0.075   10   .  .  .  .  .  .  .  .
  0.1    14   . 5   5  4  5  5  5  .  .
  0.125   10   .  .  .  .  .  .  .  .
  0.15    10   .  .  .  .  .  .  .  .
  0.2      .
  0.25      .
  0.5      .
  0.75      .
  1        .
  1.5      .
  2        .

```

Padilla's data are from an acute study, with multiple doses at one time point, and multiple timepoints for 1 mg/kg. Mrids 44254401, 44420301, and 44472001 are acute studies. The only dose at which there is a useful time course in adults is at 1 mg/kg, in both the Padilla study and 44472001. The new study 46615301 has a time course study in pnd11 animals conducted at 0.1 mg/kg. The earliest time point in any study is 0.5 hour after dosing, and all the dose-response data sets include this time point. Some also include later (some, much later) time points.

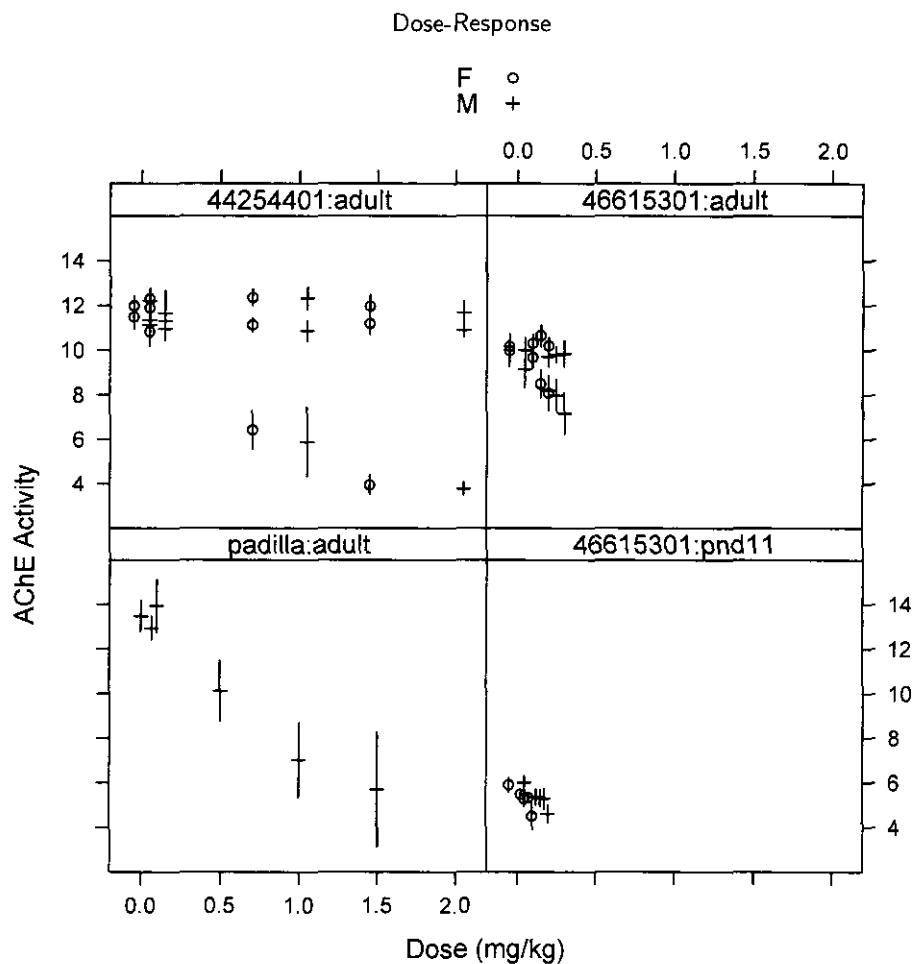
Create some new factors, for splitting up the background parameters and allowing groups to have different variances.

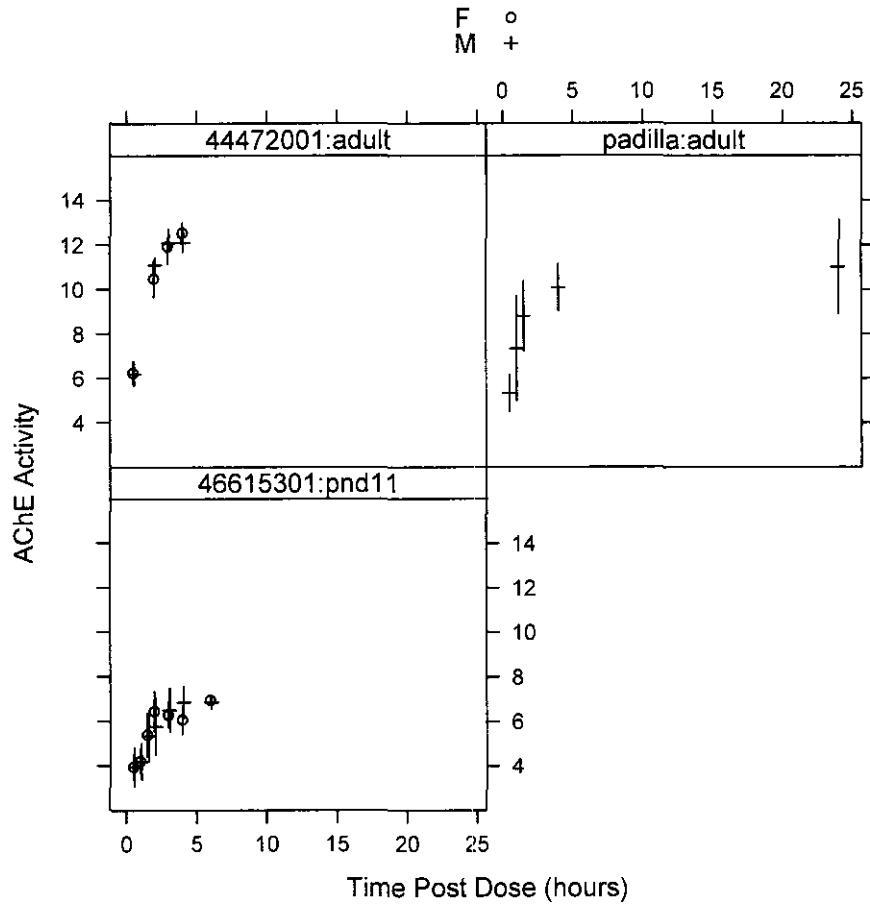
```
> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE, sep = ":"))  
> dta$mridXsexXtmpstds <- with(dta, interaction(mrid, sex, tmpstds, drop = TRUE, sep = ":"))
```

2 Dose-Response Modeling

2.1 A Quick Look at the Data

```
> dta$cells <- with(dta, interaction(mrid, age, sex, dose, tmpstds, type, drop = TRUE, sep = ":"))  
> tmp <- tapply(dta$cheact, dta$cells, function(x) c(mean(x), sd(x), length(x)))  
> nm <- names(tmp)  
> tmp <- matrix(unlist(tmp), ncol = 3, byrow = TRUE)  
> rownames(tmp) <- nm  
> nmmx <- matrix(unlist(strsplit(nm, ":")), ncol = 6, byrow = TRUE)  
> dta.summ <- data.frame(chelower = ifelse(tmp[, 3] > 1, tmp[, 1] + qt(0.025, tmp[, 3]  
+ 3)), NA), cheupper = ifelse(tmp[, 3] > 1, tmp[, 1] + qt(0.975, tmp[, 3] - 1) * tmp[, 2]/sqrt(tmp  
+ 1)), age = factor(nmmx[, 2]), sex = factor(nmmx[, 3]), dose = as.numeric(nmmx[, 4]), tmpstds = as  
+ 5), type = factor(nmmx[, 6]))
```





Time Course

Apparently, the response is already increasing at the 30 minute time point, so the time to peak effect is not greater than 30 minutes for brain AChE inhibition.

2.2 strategy

There are two sets of goals for this analysis. For all the adult data, we need an estimate for the dose that would result in 10% brain AChE inhibition (the benchmark dose, BMD), as well as an estimate of the half-life of recovery from peak inhibition. For the study that contains both adult and pnd11 animals, we want an estimate of age-specific BMD, and the ratio of adult to pnd11 BMD, and the age-specific half-life. Thus, two analyses are required: one of all the adult data, and the other of all the data from MRID 46615301.

Each analysis will proceed in a similar fashion. First, how do we handle the controls? There are typically controls at each time point for studies of recovery. If the control values are homogeneous, then it will simplify the analysis to fit a common control value across all time points for each study. If the control values are heterogeneous, then we assume that the concurrent control is the appropriate point of comparison for the activity in a dose group, so a factor needs to be set up to allow control values to vary across time points. The EPA study has a single animal per time point in the time-course study, so the critical questions for that study will be:

- is there a time-related trend among the controls?
- is the variance among the time-course controls significantly greater than that among the dose-response controls?
- does the mean time-course control value differ significantly from the mean dose-response control value.

In 44472001, there is a control group for each time. For this study the questions will be, for each sex: do the two time-course controls differ?

In the pnd11 animals of 46615301, there are concurrent controls for only some of the time points. Thus, in addition to determining whether the controls are heterogeneous across time, if the answer is "yes", then we need to determine how to set a control level for each time point.

In the registrant-submitted studies, we will maintain differences between sex and age, at the least.

The remaining dose-response parameters are initially allowed to vary among MRID and sex (and age, when appropriate), to the extent possible for the design (in particular, the recovery half-life can only be estimated in studies where there is a recovery component). Once a model is fit, Wald type tests are used to collapse the initial richly parameterized model to a simpler one; for example, if the data do not support allowing lg to vary among studies or sexes, fitting a simpler parameterization.

The dose-response parameters, ID , lg , and tz may not be estimable with the data at hand. In particular, it is generally not possible to estimate tz , unless doses are so great that the response has reached its asymptotic value. In the course of getting initial values for these parameters, if it is clear that tz cannot be estimated, it is fixed at -10 , which sets the maximum possible inhibition level to be nearly 100%.

2.3 How Heterogeneous are the Time Course Controls?

The EPA dataset has just one animal per time point in the time course control group. We can do tests there to determine whether there is any additional variability among times: regression of response on time among the controls to look for trends, and comparison of the variance among times to the variance among the control animals from the dose-response portion of the study. We do these tests here. First, regression of the responses on time:

```
> with(subset(dta, mrnid == "padilla" & dose == 0 & type == "timecourse"), {
+   print(summary(lm(cheact ~ tmpstds)))
+ })
```

Call:

```
lm(formula = cheact ~ tmpstds)
```

Residuals:

| 1 | 2 | 3 | 4 | 5 |
|----------|---------|----------|---------|----------|
| -0.63887 | 0.71780 | -0.10253 | 0.04055 | -0.01695 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|----------------|----------|------------|---------|--------------|
| (Intercept) | 10.17109 | 0.30352 | 33.511 | 5.84e-05 *** |
| tmpstds | 0.04875 | 0.02781 | 1.753 | 0.178 |
| --- | | | | |
| Signif. codes: | 0 | *** | 0.001 | ** |
| | | | 0.01 | * |
| | | | 0.05 | . |
| | | | 0.1 | S |
| | | | 1 | S |

Residual standard error: 0.5585 on 3 degrees of freedom

Multiple R-squared: 0.506, Adjusted R-squared: 0.3414

F-statistic: 3.073 on 1 and 3 DF, p-value: 0.1779

The test for trend is the significance of the coefficient for $tmpstds$. The P-value is 0.178, so there is no evidence for a trend. Now, compare the variances among the time course controls with the dose-response controls:

```
> with(subset(dta, mrnid == "padilla" & dose == 0), {
+   tc <- cheact[type == "timecourse"]
+   dr <- cheact[type == "doseresponse"]
+   var.test(tc, dr)
+ })
```

F test to compare two variances

```
data: tc and dr
F = 1.5082, num df = 4, denom df = 4, p-value = 0.7002
alternative hypothesis: true ratio of variances is not equal to 1
95 percent confidence interval:
 0.1570307 14.4856120
sample estimates:
ratio of variances
 1.508206
```

There is no reason to think there is added variability among the time-course controls. Finally, are the two control groups different from each other?

```
> with(subset(dta, mrid == "padilla" & dose == 0), {
+   tc <- cheact[type == "timecourse"]
+   dr <- cheact[type == "doseresponse"]
+   t.test(tc, dr)
+ })
```

Welch Two Sample t-test

```
data: tc and dr
t = -7.5155, df = 7.685, p-value = 8.422e-05
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-3.904777 -2.061094
sample estimates:
mean of x mean of y
 10.47337 13.45630
```

The time course and dose-response controls differ from each other, so use a separate control value for the dose-response and time-course portions of that study (that is, use a two values of 1A for the entire EPA dataset).

Next, how heterogeneous are the controls in 44472001? We test for both trend and heterogeneity:

```
> with(subset(dta, mrid == "44472001" & dose == 0), {
+   print(summary(lm(cheact ~ sex + tmpstds + tmpstds:sex)))
+   print(summary(lm(cheact ~ sex + tmpstds)))
+   out1 <- lm(cheact ~ sex * factor(tmpstds))
+   out2 <- lm(cheact ~ sex + factor(tmpstds))
+   print(anova(out1, out2, test = "F"))
+ })
```

Call:
`lm(formula = cheact ~ sex + tmpstds + tmpstds:sex)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -1.15523 | -0.41188 | -0.04461 | 0.31723 | 2.14394 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|------------|
| (Intercept) | 11.89364 | 0.20847 | 57.051 | <2e-16 *** |
| sexM | -0.58234 | 0.29483 | -1.975 | 0.0519 . |
| tmpstds | 0.13215 | 0.07709 | 1.714 | 0.0906 . |

```

sexM:tmpstds  0.01888    0.10903   0.173   0.8630
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1  .

```

Residual standard error: 0.6304 on 76 degrees of freedom
 Multiple R-squared: 0.219, Adjusted R-squared: 0.1882
 F-statistic: 7.104 on 3 and 76 DF, p-value: 0.0002857

Call:
`lm(formula = cheact ~ sex + tmpstds)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -1.13989 | -0.40095 | -0.03753 | 0.31310 | 2.14984 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|--------------|
| (Intercept) | 11.87123 | 0.16237 | 73.114 | < 2e-16 *** |
| sexM | -0.53750 | 0.14008 | -3.837 | 0.000253 *** |
| tmpstds | 0.14159 | 0.05417 | 2.614 | 0.010764 * |

 Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 .

Residual standard error: 0.6265 on 77 degrees of freedom
 Multiple R-squared: 0.2187, Adjusted R-squared: 0.1984
 F-statistic: 10.78 on 2 and 77 DF, p-value: 7.469e-05

Analysis of Variance Table

Model 1: cheact ~ sex * factor(tmpstds)
 Model 2: cheact ~ sex + factor(tmpstds)

| Res.Df | RSS | Df | Sum of Sq | F | Pr(>F) |
|--------|-----|---------|-----------|---------|------------------|
| 1 | 72 | 25.0959 | | | |
| 2 | 75 | 28.6143 | -3 | -3.5184 | 3.3647 0.02321 * |

 Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 .

There is a significantly increasing linear trend that does not differ between the sexes, and some evidence of interaction between time and sex in the variability of the means. For this study, we keep a separate control value for each sex and time.

Finally, the controls for the pnd11 animals of 46615301. We combine the timecourse and dose-response portions, because the 0.5 hour control timepoint is just in the dose-response portion of the study.

```

> with(subset(dta, mrid == "46615301" & age == "pnd11" & dose == 0), {
+   print(summary(lm(cheact ~ sex + tmpstds + tmpstds:sex)))
+   print(summary(lm(cheact ~ sex + tmpstds)))
+   out1 <- lm(cheact ~ sex * factor(tmpstds))
+   out2 <- lm(cheact ~ sex + factor(tmpstds))
+   print(anova(out1, out2, test = "F"))
+   print(summary(out2))
+ })

```

Call:
`lm(formula = cheact ~ sex + tmpstds + tmpstds:sex)`

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|----------|----------|---------|---------|---------|
| | -1.67931 | -0.33397 | 0.08126 | 0.33989 | 1.09954 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|--------------|----------|------------|---------|-------------|
| (Intercept) | 5.50690 | 0.18538 | 29.706 | < 2e-16 *** |
| sexM | 0.25126 | 0.26217 | 0.958 | 0.34287 |
| tmpstds | 0.30069 | 0.08940 | 3.363 | 0.00156 ** |
| sexM:tmpstds | -0.07954 | 0.12643 | -0.629 | 0.53238 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 . 1

Residual standard error: 0.5896 on 46 degrees of freedom
 Multiple R-squared: 0.2811, Adjusted R-squared: 0.2342
 F-statistic: 5.995 on 3 and 46 DF, p-value: 0.001548

Call:

```
lm(formula = cheact ~ sex + tmpstds)
```

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|---------|---------|--------|--------|--------|
| | -1.6554 | -0.3853 | 0.0804 | 0.3560 | 1.0836 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|--------------|
| (Intercept) | 5.57053 | 0.15436 | 36.089 | < 2e-16 *** |
| sexM | 0.12400 | 0.16570 | 0.748 | 0.457973 |
| tmpstds | 0.26092 | 0.06281 | 4.154 | 0.000137 *** |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 . 1

Residual standard error: 0.5858 on 47 degrees of freedom
 Multiple R-squared: 0.2749, Adjusted R-squared: 0.244
 F-statistic: 8.909 on 2 and 47 DF, p-value: 0.0005241

Analysis of Variance Table

```
Model 1: cheact ~ sex * factor(tmpstds)
Model 2: cheact ~ sex + factor(tmpstds)
  Res.Df   RSS Df Sum of Sq    F Pr(>F)
  1     42  8.9880
  2     45  9.6788 -3   -0.6908 1.076 0.3696
```

Call:

```
lm(formula = cheact ~ sex + factor(tmpstds))
```

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|---------|---------|---------|--------|--------|
| | -1.0880 | -0.2495 | -0.0200 | 0.2995 | 0.8980 |

Coefficients:

```

          Estimate Std. Error t value Pr(>|t|)
(Intercept)      5.8680    0.1227  47.823 < 2e-16 ***
sexM            0.1240    0.1312   0.945 0.349551
factor(tmpstds)1 -0.6900    0.1796  -3.841 0.000381 ***
factor(tmpstds)2  0.6200    0.1796   3.452 0.001223 **
factor(tmpstds)4  0.6700    0.1796   3.730 0.000534 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Residual standard error: 0.4638 on 45 degrees of freedom
 Multiple R-squared: 0.5649, Adjusted R-squared: 0.5262
 F-statistic: 14.61 on 4 and 45 DF, p-value: 1.012e-07

Do the 0.1 mg/kg time course group at 0.5 hour differ from the 0.1 mg/kg dose-response group at 0.5 hour? If not, assign the same control group at that time to both groups:

```

> with(subset(dta, mrid == "46615301" & age == "pnd11" & dose == 0.1), {
+   print(summary(lm(cheact ~ type * sex)))
+   print(summary(lm(cheact ~ type + sex)))
+ })

```

Call:
`lm(formula = cheact ~ type * sex)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -2.2939 | -0.8418 | 0.1250 | 0.9070 | 1.9061 |

Coefficients:

```

          Estimate Std. Error t value Pr(>|t|)
(Intercept)      5.26000    0.35486  14.823 <2e-16 ***
typetimecourse  0.36571    0.40238   0.909   0.366
sexM            0.03000    0.50185   0.060   0.952
typetimecourse:sexM 0.03823    0.57096   0.067   0.947
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Residual standard error: 1.122 on 84 degrees of freedom
 Multiple R-squared: 0.02183, Adjusted R-squared: -0.01311
 F-statistic: 0.6248 on 3 and 84 DF, p-value: 0.601

Call:
`lm(formula = cheact ~ type + sex)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -2.2895 | -0.8486 | 0.1250 | 0.9105 | 1.9105 |

Coefficients:

```

          Estimate Std. Error t value Pr(>|t|)
(Intercept)      5.24523    0.27637  18.979 <2e-16 ***
typetimecourse  0.38470    0.28380   1.356   0.179
sexM            0.05953    0.23792   0.250   0.803
---

```

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 1.116 on 85 degrees of freedom
 Multiple R-squared: 0.02177, Adjusted R-squared: -0.001242
 F-statistic: 0.946 on 2 and 85 DF, p-value: 0.3923

The controls are heterogeneous, with an upward trend with increasing time that does not differ between the sexes. The first two outputs copied above tell that story. However, this does not tell the whole story. When we treat time post dose as a factor, we see again that the sexes do not differ, but the means do not change linearly with time. In the last output above, the (Intercept) term is the mean for the 0.5 hour females, and their terms factor(tmpstds)1, etc. are differences between the (in this case) 1 hour time point and the 0.5 hour time point. There is a significant, roughly 10%, drop from 0.5 hour to 1 hour, then, at 2 and 4 hours, the means are roughly 10% greater than the 0.5 hour mean. All these differences are individually significant; that is, the differences are much greater than would be expected from the sampling variability.

The following code sets up a factor to handle the control values we need:

```
> dta$Controls <- with(dta, interaction(mrid, sex, age, type, tmpstds, drop = TRUE, sep = ":"))  

> lvls <- levels(dta$Controls)  

> lvls[grep("^\$padilla.*timecourse", lvls)] <- "padilla:timecourse"  

> lvls[grep("^\$padilla.*doseresponse", lvls)] <- "padilla:doseresponse"  

> lvls <- sub("(46615301:(F|M):pnd11:timecourse:)((1.5)/(3)/(6))", "\\1missing", lvls)  

> lvls <- sub("(46615301:(F|M):pnd11:)timecourse(:0.5)", "\\1doseresponse\\3", lvls)  

> levels(dta$Controls) <- lvls
```

2.4 Levels for tz, lg, 1D, and 1Tr

The log benchmark dose, 1D, will have a random component (among mrids) in the final analysis, and in addition, will take on different values by sex and age. This may be collapsed after testing for differences between sexes, and contrasts between ages will be calculated. Since only the dose-response portions of the data provide information about 1D, we need to pair the one time-course-only mrid (44472001) with a dose-response mrid. This will be (somewhat arbitrarily) 44254401

Whether we can estimate values for lg and/or tz at all depends critically on the experimental design. In particular, unless the doses are great enough that inhibition approaches a plateau, tz will not be well identified. If there are no doses low enough to determine a low-dose plateau, lg will be governed by the shape of the dose-response curve at higher doses, as the response levels out with increasing dose. In that case, experience shows that lg and tz are strongly confounded. The plots of the adult dose-response data above suggest that lg may be positive, and that the dose-response *may* be beginning to level off at the higher doses. There are certainly not enough data to estimate separate values of lg and tz for each dataset, but we may be able to borrow across datasets. So, we will try fitting gender-specific values for these two parameters, pooling across all adult datasets. When we compare adult to pnd11 values in 46615301, we will just set tz = -10, as there is clearly no way to estimate that parameter from these data, as the doses in that study are too low to allow the response to even begin to plateau.

The (log) half-life parameter, 1Tr, is estimable in adults from two datasets. Rather than assign dose-response datasets to one or the other time-course dataset, we just estimate a pooled value over the whole set of data for each sex.

Finally, estimate a separate variance constant for each study X sex combination. Setup of factors to allow the above:

```
> dta$mrid2 <- dta$mrid  

> lvls <- levels(dta$mrid)  

> lvls[lvls == "44472001"] <- "44254401"  

> levels(dta$mrid2) <- lvls  

> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE, sep = ":"))
```

3 Adult Dose-Response Modeling

3.1 strategy

Use the model with simple exponential recovery (`tcmfn4()`). It looks as if the time to peak effect for all these chemicals is likely to be less than a half-hour, so the exponential recovery model is probably indistinguishable from the one with the more complex time course.

Fitting the model will follow these steps:

1. First, use `GetInitialValues()` to get starting values for the model against these data, and determine whether we can estimate `lg` and `tz` of the dose-response parameters.
2. Next, fit `tcmfn4()` using the parameterizations determined in the previous step. Since there are three data sets, use `nlme()`, with a random effect for `mrid`. Both time course studies were done at about the same dose, so fit a single value for `lTr` (initially, for each sex and `mrid`).

Set up an adult-only dataset:

```
> dta.a <- CleanUp(subset(dta, age == "adult"))
```

3.2 Initial Values

Save the initial values so that we do not need to go through all this to re-run the analysis. Also, set the argument `delta` to 0.5, the earliest non-zero time point.

```
> formals(tcmfn4)$delta <- min(dta$tmpstds[dta$tmpstds > 0])
> initfile <- paste("initvals-brain-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+   lA.start <- lm(I(log(cheact)) ~ Controls - 1, data = CleanUp(subset(dta.a, dose %in% 0)))
+   Start <- c(coef(lA.start), rep(log(0.2), nlevels(dta.a$sex)), rep(log(0.15), nlevels(dta.a$mridXs)
+     nlevels(dta.a$sex)), rep(log(1.5), nlevels(dta.a$sex)))
+   init1 <- GetInitialValues(cheact ~ tcmfn4(dose, tmpstds, lA = lA, tz = tz, lD = lD, lg = lg, lTr
+     params = list(lA ~ Controls - 1, tz ~ sex - 1, lD ~ mridXsex - 1, lg ~ sex - 1, lTr ~ sex - 1
+     weights = varComb(varIdent(form = ~1 / mridXsex), varPower(value = 1)))
+   save(init1, file = initfile)
+ } else load(initfile)
> tmp <- t(init1$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:5], digits = 2)
```

| | [,1] | [,2] | [,3] | [,4] | [,5] |
|-----------------------|-------|-------|------|------|------|
| CondIndex | 45.74 | 22.60 | 7.85 | 6.71 | 4.45 |
| mu | 0.04 | 0.08 | 0.24 | 0.28 | 0.43 |
| tz.sexF | 0.01 | 0.00 | 0.91 | 0.00 | 0.00 |
| tz.sexM | 0.00 | 0.28 | 0.00 | 0.57 | 0.00 |
| lD.mridXsex44254401:F | 0.99 | 0.00 | 0.00 | 0.00 | 0.00 |
| lD.mridXsex44472001:F | 0.99 | 0.00 | 0.00 | 0.00 | 0.00 |
| lD.mridXsex46615301:F | 0.74 | 0.00 | 0.00 | 0.00 | 0.00 |
| lD.mridXsex44254401:M | 0.00 | 0.89 | 0.00 | 0.01 | 0.00 |
| lD.mridXsex44472001:M | 0.00 | 0.89 | 0.00 | 0.00 | 0.00 |
| lD.mridXsexpadilla:M | 0.00 | 0.97 | 0.00 | 0.01 | 0.00 |
| lD.mridXsex46615301:M | 0.00 | 0.19 | 0.00 | 0.00 | 0.73 |
| lg.sexF | 1.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| lg.sexM | 0.00 | 0.99 | 0.00 | 0.00 | 0.00 |
| lTr.sexF | 0.00 | 0.00 | 0.96 | 0.00 | 0.00 |
| lTr.sexM | 0.00 | 0.02 | 0.00 | 0.91 | 0.00 |

```

> init1$start$beta

1A.Controls46615301:F:adult:doseresponse:0.5 1A.Controls46615301:M:adult:doseresponse:0.5 1A.Controls
                                         2.3050864                                     2.2203977
1A.Controls44472001:M:adult:timecourse:0.5          1A.Controlspadilla:timecourse
                                         2.4035198                                     2.3809061
1A.Controls44254401:F:adult:doseresponse:1 1A.Controls44254401:M:adult:doseresponse:1 1A.Contro
                                         2.4772793                                     2.4123406
1A.Controls44472001:M:adult:timecourse:2 1A.Controls44472001:F:adult:timecourse:3 1A.Contro
                                         2.5107231                                     2.5281572
1A.Controls46615301:F:adult:doseresponse:4 1A.Controls46615301:M:adult:doseresponse:4 1A.Contro
                                         2.3403826                                     2.2917047
1A.Controls44472001:M:adult:timecourse:4 1A.Controls44254401:F:adult:doseresponse:24 1A.Controls4
                                         2.4895579                                     2.4973288
1A.Controls44254401:F:adult:doseresponse:360 1A.Controls44254401:M:adult:doseresponse:360
                                         2.4121117                                     2.4076197
                                         tz.sexM
                                         -38.5157680                                     1D.mridXsex44254401:F
                                         -1.2329021
                                         1D.mridXsex46615301:F
                                         -1.6905656                                     1D.mridXsex44254401:M
                                         -1.8938615
                                         1D.mridXsexpadilla:M
                                         -1.4155363                                     1D.mridXsex46615301:M
                                         -1.9778174
                                         lg.sexM
                                         0.2759736                                     lTr.sexF
                                         -0.1659953

```

The above shows the results of a redundancy analysis. tz is pushed by the optimization to very small values (about -33), which generally results in numerical problems, and is consistent with essentially no positive horizontal asymptote. So, fix tz to -10, and re-estimate:

```

> formals(tcfn4)$delta <- min(dta$tmpstds[dta$tmpstds > 0])
> formals(tcfn4)$tz <- -10
> initfile <- paste("initvals-brain-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+   Start <- init1$start$beta
+   Start <- Start[-grep("tz", names(Start))]
+   init2 <- GetInitialValues(cheact ~ tcfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, lTr = lTr), d
+     Controls - 1, 1D ~ mridXsex - 1, lg ~ sex - 1, lTr ~ sex - 1), start = Start, weights = varCo
+     mridXsex), varPower(value = 1)))
+   save(init2, file = initfile)
+ } else load(initfile)
> tmp <- t(init2$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^\u0331", rownames(tmp)), ]
> round(tmp[, 1:5], digits = 2)

[.1]  [.2]  [.3]  [.4]  [.5]
CondIndex      42.31 17.55 4.04 3.84 3.52
mu            0.04  0.10 0.43 0.45 0.49
1D.mridXsex44254401:F 0.99  0.00 0.00 0.00 0.00
1D.mridXsex44472001:F 0.99  0.00 0.00 0.00 0.00
1D.mridXsex46615301:F 0.74  0.00 0.00 0.00 0.23
1D.mridXsex44254401:M 0.00  0.84 0.00 0.12 0.00
1D.mridXsex44472001:M 0.00  0.86 0.00 0.00 0.00
1D.mridXsexpadilla:M  0.00  0.97 0.00 0.00 0.00
1D.mridXsex46615301:M 0.00  0.15 0.76 0.01 0.00
lg.sexF        1.00  0.00 0.00 0.00 0.00

```

```

lg.sexM          0.00  0.99 0.00 0.00 0.00
lTr.sexF         0.06  0.00 0.00 0.00 0.00
lTr.sexM         0.00  0.18 0.01 0.69 0.00

> init2$start$beta

1A.Controls46615301:F:adult:doseresponse:0.5 1A.Controls46615301:M:adult:doseresponse:0.5 1A.Controls
                                                 2.3042130                           2.2208293
1A.Controls44472001:M:adult:timecourse:0.5           1A.Controlspadilla:timecourse
                                                 2.4068840                           2.3791662
1A.Controls44254401:F:adult:doseresponse:1 1A.Controls44254401:M:adult:doseresponse:1 1A.Conto
                                                 2.4767856                           2.4120349
1A.Controls44472001:M:adult:timecourse:2 1A.Controls44472001:F:adult:timecourse:3 1A.Conto
                                                 2.5037978                           2.5263026
1A.Controls46615301:F:adult:doseresponse:4 1A.Controls46615301:M:adult:doseresponse:4 1A.Conto
                                                 2.3402287                           2.2921778
1A.Controls44472001:M:adult:timecourse:4 1A.Controls44254401:F:adult:doseresponse:24 1A.Controls4
                                                 2.4870001                           2.4973291
1A.Controls44254401:F:adult:doseresponse:360 1A.Controls44254401:M:adult:doseresponse:360
                                                 2.4121117                           2.4076208
1D.mridXsex44472001:F                         1D.mridXsex46615301:F
                                                 -0.7179841                          -1.6884315
1D.mridXsex44472001:M                         1D.mridXsexpadilla:M
                                                 -1.2867253                          -1.4256345
                                                 lg.sexF                            lg.sexM
                                                 0.9327761                          0.2668033
                                                 lTr.sexM
                                                 -0.1177363

> Start <- Start0 <- init2$start$beta
> tmp <- getParms("^1D", Start)
> mx <- t(sapply(strsplit(names(tmp), ":"), function(x) x[1:2]))
> mx[, 1] <- gsub("1D\\\.mridXsex", "", mx[, 1])
> tdta <- data.frame(coef = as.vector(tmp), mrid = factor(mx[, 1]), sex = factor(mx[, 2]))
> lvls <- levels(tdta$mrid)
> tdta$mrid2 <- tdta$mrid
> lvls[lvls == "44472001"] <- "44254401"
> levels(tdta$mrid2) <- lvls
> 1Dstart <- coef(lm(coef ~ 0 + sex, data = tdta))
> Start <- c(getParms("^1A", Start), 1Dstart, getParms("^lg", Start), getParms("^lTr", Start))
> tdta$res <- resid(lm(coef ~ 0 + sex, data = tdta))
> rout <- coef(lm(res ~ 0 + mrid2, data = tdta))
> Start <- list(fixed = Start, random = matrix(rout - mean(rout), nrow = length(rout), ncol = 1, dimnam
+     "", names(rout)), "1D"))
> if (file.exists("RatBraindrmod2.RData")) {
+   load("RatBraindrmod2.RData")
+ } else {
+   icnt <- 1
+   Maxcnt <- 50
+   repeat {
+     drmod2 <- try(nlme(cheact ~ tcfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, lTr = lTr), data
+       Controls ~ 1, 1D ~ sex ~ 1, lg ~ sex ~ 1, lTr ~ sex ~ 1), random = 1D ~ 1 / mrid2, weight
+       mridXsex), varPower(value = 1)), start = Start), silent = TRUE)
+     if (!inherits(drmod2, "try-error") || icnt > Maxcnt) {
+       if (icnt <= Maxcnt)

```

```

+
+           writeLines(paste("Successful in ", icnt, if (icnt > 1)
+                         "tries"
+                         else "try"))
+           else writeLines("Maxcnt exceeded")
+           break
+
+       }
+       icnt <- icnt + 1
+       Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+
+   }
+   save(drmod2, file = "RatBraindrmod2.RData")
+ }
> drmod2

Nonlinear mixed-effects model fit by maximum likelihood
Model: cheact ~ tcmlfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, lTr = lTr)
Data: dta.a
Log-likelihood: -778.6022
Fixed: list(lA ~ Controls - 1, 1D ~ sex - 1, lg ~ sex - 1, lTr ~ sex - 1)
1A.Controls46615301:F:adult:doseresponse:0.5 1A.Controls46615301:M:adult:doseresponse:0.5 1A.Controls
2.3074283 2.1695385
1A.Controls44472001:M:adult:timecourse:0.5 1A.Controlspadilla:timecourse
2.4305050 2.3602484
1A.Controls44254401:F:adult:doseresponse:1 1A.Controls44254401:M:adult:doseresponse:1 1A.Contro
2.4824204 2.3755537
1A.Controls44472001:M:adult:timecourse:2 1A.Controls44472001:F:adult:timecourse:3 1A.Contro
2.4800487 2.5197686
1A.Controls46615301:F:adult:doseresponse:4 1A.Controls46615301:M:adult:doseresponse:4 1A.Contro
2.3363443 2.2854076
1A.Controls44472001:M:adult:timecourse:4 1A.Controls44254401:F:adult:doseresponse:24 1A.Controls4
2.4778705 2.4973292
1A.Controls44254401:F:adult:doseresponse:360 1A.Controls44254401:M:adult:doseresponse:360
2.4121119 2.4076206
1D.sexM lg.sexF
-1.5243531 0.6202895
lTr.sexF lTr.sexM
-0.4987362 -0.4493743

Random effects:
Formula: 1D ~ 1 | mrid2
1D.(Intercept) Residual
StdDev: 2.735315e-05 8.021784

Combination of variance functions:
Structure: Different standard deviations per stratum
Formula: ~1 | mridXsex
Parameter estimates:
44254401:M 44254401:F 44472001:M 44472001:F padilla:M 46615301:M 46615301:F
1.0000000 0.7245427 0.6808252 0.8093323 0.9614803 0.7569098 0.7034310
Structure: Power of variance covariate
Formula: ~fitted()
Parameter estimates:
power
-0.8836457
Number of Observations: 615

```

Number of Groups: 3

Are the sex differences significant? If not, refit the simpler model.

```
> L <- structure(c(1, -1), names = c("1D.sexF", "1D.sexM"))
> anova(drmmod2, L = L)

F-test for linear combination(s)
1D.sexF 1D.sexM
  1      -1
  numDF denDF  F-value p-value
1       1    587  0.9724597  0.3245

> L <- structure(c(1, -1), names = c("lg.sexF", "lg.sexM"))
> anova(drmmod2, L = L)

F-test for linear combination(s)
lg.sexF lg.sexM
  1      -1
  numDF denDF  F-value p-value
1       1    587  4.153118   0.042

> L <- structure(c(1, -1), names = c("lTr.sexF", "lTr.sexM"))
> anova(drmmod2, L = L)

F-test for linear combination(s)
lTr.sexF lTr.sexM
  1      -1
  numDF denDF  F-value p-value
1       1    587  0.1513022  0.6974
```

The only parameter that differs between the sexes is the log power, lg.

Now test the composite hypothesis, that 1D and lTr, do not differ between the sexes:

```
> print(anova(drmmod2, L = matrix(c(1, -1, 0, 0, 0, 0, 1, -1), byrow = TRUE, nrow = 2, ncol = 4, dimnames =
+           "1D.sexM", "lTr.sexF", "lTr.sexM"))))

F-test for linear combination(s)
1D.sexF 1D.sexM lTr.sexF lTr.sexM
  1      1      -1      0      0
  2      0      0      1     -1
  numDF denDF  F-value p-value
1       2    587  0.6089823  0.5442

> Start <- drmod2$coefficients$fixed
> Start <- Start0 <- c(getParms("^1A", Start), mean(getParms("^1D", Start)), getParms("^lg", Start), me
+   Start))
> lvls <- levels(tdt$mrnid)
> tdt$mrnid2 <- tdt$mrnid
> lvls[lvls == "44472001"] <- "44254401"
> levels(tdt$mrnid2) <- lvls
> if (file.exists("RatBraindrmod3.RData")) {
+   load("RatBraindrmod3.RData")
+ } else {
+   icnt <- 1
+   Maxcnt <- 50
+   repeat {
```

```

+
+     drmod3 <- try(nlme(cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data =
+                         Controls ~ 1, lD ~ 1, lg ~ sex ~ 1, lTr ~ 1), random = lD ~ 1 | mrid2, weights = varComb(
+                           mridXsex), varPower(value = 1)), start = Start), silent = TRUE)
+     if (!inherits(drmod3, "try-error") || icnt > Maxcnt) {
+       if (icnt <= Maxcnt)
+         writeLines(paste("Successful in ", icnt, if (icnt > 1)
+                           "tries"
+                           else "try"))
+       else writeLines("Maxcnt exceeded")
+       break
+     }
+     icnt <- icnt + 1
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+   }
+   save(drmod3, file = "RatBraindrmod3.RData")
+ }
> drmod3

```

Nonlinear mixed-effects model fit by maximum likelihood

Model: cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)

Data: dta.a

Log-likelihood: -779.1021

Fixed: list(lA ~ Controls ~ 1, lD ~ 1, lg ~ sex ~ 1, lTr ~ 1)

| | | |
|--|--|--------------|
| lA.Controls46615301:F:adult:doseresponse:0.5 | lA.Controls46615301:M:adult:doseresponse:0.5 | lA.Controls |
| 2.2994567 | 2.1848697 | |
| lA.Controls44472001:M:adult:timecourse:0.5 | lA.Controlspadilla:timecourse | |
| 2.4307541 | 2.3595438 | |
| lA.Controls44254401:F:adult:doseresponse:1 | lA.Controls44254401:M:adult:doseresponse:1 | lA.Contro |
| 2.4817099 | 2.3763071 | |
| lA.Controls44472001:M:adult:timecourse:2 | lA.Controls44472001:F:adult:timecourse:3 | lA.Contro |
| 2.4784217 | 2.5206511 | |
| lA.Controls46615301:F:adult:doseresponse:4 | lA.Controls46615301:M:adult:doseresponse:4 | lA.Contro |
| 2.3362840 | 2.2855062 | |
| lA.Controls44472001:M:adult:timecourse:4 | lA.Controls44254401:F:adult:doseresponse:24 | lA.Controls4 |
| 2.4772606 | 2.4973292 | |
| lA.Controls44254401:F:adult:doseresponse:360 | lA.Controls44254401:M:adult:doseresponse:360 | |
| 2.4121119 | 2.4076206 | |
| lg.sexF | lg.sexM | |
| 0.6487645 | 0.1793810 | |

Random effects:

Formula: lD ~ 1 | mrid2
 lD Residual
 StdDev: 1.849291e-05 8.493617

Combination of variance functions:

Structure: Different standard deviations per stratum

Formula: ~1 | mridXsex

Parameter estimates:

44254401:M 44254401:F 44472001:M 44472001:F padilla:M 46615301:M 46615301:F
 1.0000000 0.7130351 0.6722112 0.8034391 0.9492855 0.7361128 0.6965392

Structure: Power of variance covariate

Formula: ~fitted(.)

Parameter estimates:

```

power
-0.9030996
Number of Observations: 615
Number of Groups: 3

```

Now can we collapse lg?

```

> L <- structure(c(1, -1), names = c("lg.sexF", "lg.sexM"))
> anova(drmmod3, L = L)

```

```

F-test for linear combination(s)
lg.sexF lg.sexM
 1      -1
numDF denDF  F-value p-value
1       1   589 43.05407 <.0001

```

No. The model in drmod3 is what we will use.

```

> Ints.a <- intervals(drmmod3, which = "fixed")$fixed
> Ints90.a <- intervals(drmmod3, which = "fixed", level = 0.9)$fixed
> tTab.a <- summary(drmmod3)$tTable
> summary(drmmod3)

```

```

Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
  Data: dta.a
        AIC      BIC      logLik
  1624.204 1770.118 -779.1021

```

```

Random effects:
Formula: lD ~ 1 | mrid2
             lD Residual
StdDev: 1.849291e-05 8.493617

```

```

Combination of variance functions:
Structure: Different standard deviations per stratum
Formula: ~1 | mridXsex
Parameter estimates:
44254401:M 44254401:F 44472001:M 44472001:F padilla:M 46615301:M 46615301:F
1.0000000 0.7130351 0.6722112 0.8034391 0.9492855 0.7361128 0.6965392
Structure: Power of variance covariate
Formula: ~fitted()
Parameter estimates:

```

```

power
-0.9030996
Fixed effects: list(lA ~ Controls - 1, lD ~ 1, lg ~ sex - 1, lTr ~ 1)
                Value Std.Error DF t-value p-value
lA.Controls46615301:F:adult:doseresponse:0.5 2.2994567 0.02031927 589 113.16631 0.0000
lA.Controls46615301:M:adult:doseresponse:0.5 2.1848697 0.02051537 589 106.49918 0.0000
lA.Controls44472001:F:adult:timecourse:0.5 2.4975689 0.01898572 589 131.54990 0.0000
lA.Controls44472001:M:adult:timecourse:0.5 2.4307541 0.01778746 589 136.65550 0.0000
lA.Controlspadilla:timecourse 2.3595438 0.02237117 589 105.47251 0.0000
lA.Controlspadilla:doseresponse 2.6150144 0.01508378 589 173.36603 0.0000
lA.Controls44254401:F:adult:doseresponse:1 2.4817099 0.01253779 589 197.93842 0.0000
lA.Controls44254401:M:adult:doseresponse:1 2.3763071 0.02037395 589 116.63459 0.0000

```

| | | | | | |
|--|--------------------|--------------------|--------------------|-----------|--------|
| 1A.Controls44472001:F:adult:timecourse:2 | 2.4948699 | 0.01672534 | 589 | 149.16710 | 0.0000 |
| 1A.Controls44472001:M:adult:timecourse:2 | 2.4784217 | 0.01349573 | 589 | 183.64494 | 0.0000 |
| 1A.Controls44472001:F:adult:timecourse:3 | 2.5206511 | 0.01410873 | 589 | 178.65894 | 0.0000 |
| 1A.Controls44472001:M:adult:timecourse:3 | 2.5146355 | 0.01150796 | 589 | 218.51279 | 0.0000 |
| 1A.Controls46615301:F:adult:doseresponse:4 | 2.3362840 | 0.01123608 | 589 | 207.92703 | 0.0000 |
| 1A.Controls46615301:M:adult:doseresponse:4 | 2.2855062 | 0.01359247 | 589 | 168.14497 | 0.0000 |
| 1A.Controls44472001:F:adult:timecourse:4 | 2.5398064 | 0.01275198 | 589 | 199.16959 | 0.0000 |
| 1A.Controls44472001:M:adult:timecourse:4 | 2.4772606 | 0.01185594 | 589 | 208.94677 | 0.0000 |
| 1A.Controls44254401:F:adult:doseresponse:24 | 2.4973292 | 0.00842870 | 589 | 296.28863 | 0.0000 |
| 1A.Controls44254401:M:adult:doseresponse:24 | 2.4824035 | 0.01231640 | 589 | 201.55273 | 0.0000 |
| 1A.Controls44254401:F:adult:doseresponse:360 | 2.4121119 | 0.00991273 | 589 | 243.33474 | 0.0000 |
| 1A.Controls44254401:M:adult:doseresponse:360 | 2.4076206 | 0.01402150 | 589 | 171.70917 | 0.0000 |
| 1D | -1.6921956 | 0.10619885 | 589 | -15.93422 | 0.0000 |
| lg.sexF | 0.6487645 | 0.10514260 | 589 | 6.17033 | 0.0000 |
| lg.sexM | 0.1793810 | 0.06931863 | 589 | 2.58777 | 0.0099 |
| 1Tr | -0.4851037 | 0.06115505 | 589 | -7.93236 | 0.0000 |
| Correlation: | | | | | |
| | 1A.C46615301:F:::0 | 1A.C46615301:M:::0 | 1A.C44472001:F:::0 | 1 | |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | 0.315 | | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | 0.000 | 0.000 | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | 0.006 | 0.005 | 0.000 | | |
| 1A.Controlspadilla:timecourse | 0.017 | 0.013 | | | |
| 1A.Controlspadilla:doseresponse | 0.232 | 0.145 | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | 0.146 | 0.086 | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | 0.063 | 0.042 | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | -0.001 | 0.000 | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | 0.026 | 0.021 | | | |
| 1A.Controls44472001:F:adult:timecourse:3 | 0.007 | 0.006 | | | |
| 1A.Controls44472001:M:adult:timecourse:3 | 0.016 | 0.013 | | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | 0.021 | 0.013 | | | |
| 1A.Controls46615301:M:adult:doseresponse:4 | 0.012 | 0.008 | | | |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.005 | 0.004 | | | |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.007 | 0.006 | | | |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | | | |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | | | |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | | | |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | | | |
| 1D | -0.716 | -0.441 | | | |
| lg.sexF | -0.516 | -0.337 | | | |
| lg.sexM | -0.626 | -0.382 | | | |
| 1Tr | 0.056 | 0.047 | | | |
| | 1A.C44254401:F:::1 | 1A.C44254401:M:::1 | 1A.C44472001:F:::2 | 1 | |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | | | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | | | |
| 1A.Controlspadilla:timecourse | | | | | |
| 1A.Controlspadilla:doseresponse | | | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | 0.028 | | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | 0.055 | 0.035 | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | 0.036 | 0.054 | 0.094 | | |
| 1A.Controls44472001:F:adult:timecourse:3 | 0.040 | 0.031 | 0.098 | | |
| 1A.Controls44472001:M:adult:timecourse:3 | 0.026 | 0.034 | 0.069 | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | 0.010 | 0.007 | 0.012 | | |

| | | | |
|--|--------------------|--------------------|----------------------|
| 1A.Controls46615301:M:adult:doseresponse:4 | 0.006 | 0.005 | 0.010 |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.021 | 0.017 | 0.052 |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.012 | 0.014 | 0.032 |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1D | -0.197 | -0.092 | -0.003 |
| lg.sexF | -0.093 | -0.109 | -0.037 |
| lg.sexM | -0.190 | -0.039 | -0.057 |
| 1Tr | 0.115 | 0.117 | 0.320 |
| | 1A.C44472001:M:::3 | 1A.C46615301:F:::4 | 1A.C46615301:M:::4 1 |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | |
| 1A.Controlspadilla:timecourse | | | |
| 1A.Controlspadilla:doseresponse | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | | | |
| 1A.Controls44472001:F:adult:timecourse:3 | | | |
| 1A.Controls44472001:M:adult:timecourse:3 | | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | 0.009 | | |
| 1A.Controls46615301:M:adult:doseresponse:4 | 0.007 | 0.002 | |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.033 | 0.006 | 0.005 |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.023 | 0.004 | 0.003 |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1D | -0.031 | -0.031 | -0.018 |
| lg.sexF | -0.100 | -0.035 | -0.024 |
| lg.sexM | -0.039 | -0.033 | -0.021 |
| 1Tr | 0.217 | 0.039 | 0.032 |
| | 1A.C44254401:F:::2 | 1A.C44254401:M:::2 | 1A.C44254401:F:::3 1 |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | |
| 1A.Controlspadilla:timecourse | | | |
| 1A.Controlspadilla:doseresponse | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | | | |
| 1A.Controls44472001:F:adult:timecourse:3 | | | |
| 1A.Controls44472001:M:adult:timecourse:3 | | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | | | |
| 1A.Controls46615301:M:adult:doseresponse:4 | | | |
| 1A.Controls44472001:F:adult:timecourse:4 | | | |
| 1A.Controls44472001:M:adult:timecourse:4 | | | |
| 1A.Controls44254401:F:adult:doseresponse:24 | | | |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | | |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | |

| | | | |
|--|-------|-------|-------|
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1D | 0.000 | 0.000 | 0.000 |
| lg.sexF | 0.000 | 0.000 | 0.000 |
| lg.sexM | 0.000 | 0.000 | 0.000 |
| lTr | 0.000 | 0.000 | 0.000 |

Standardized Within-Group Residuals:

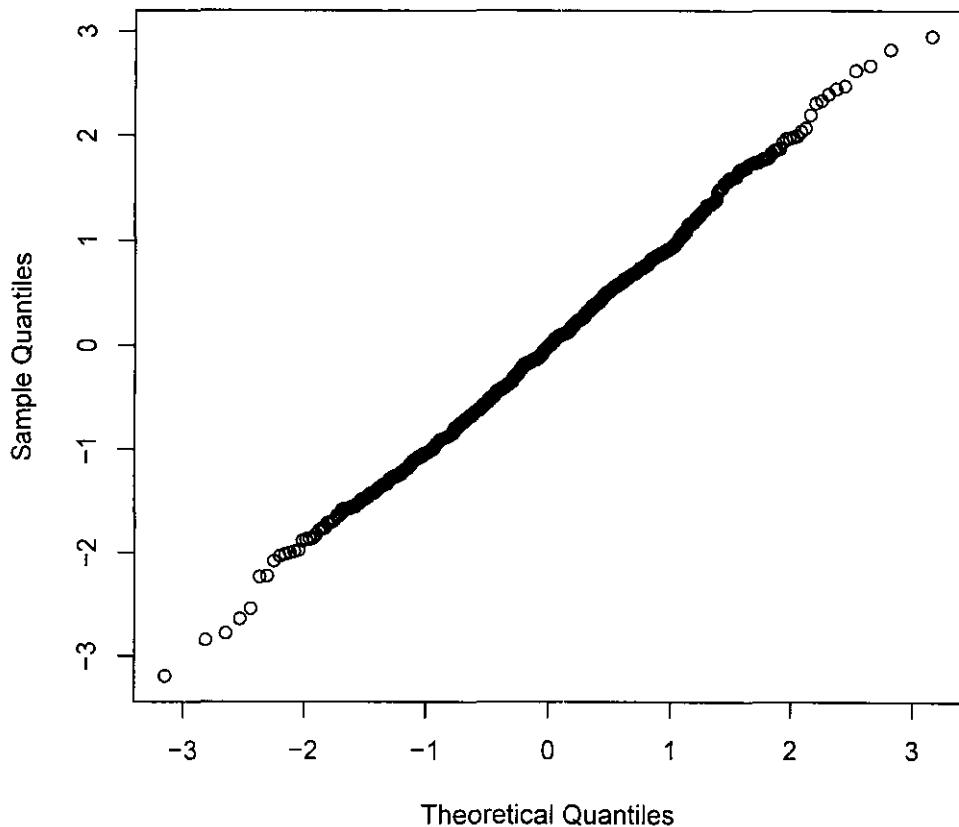
| Min | Q1 | Med | Q3 | Max |
|--------------|--------------|--------------|-------------|-------------|
| -3.190566227 | -0.702304054 | -0.002623486 | 0.668629202 | 2.951635776 |

Number of Observations: 615

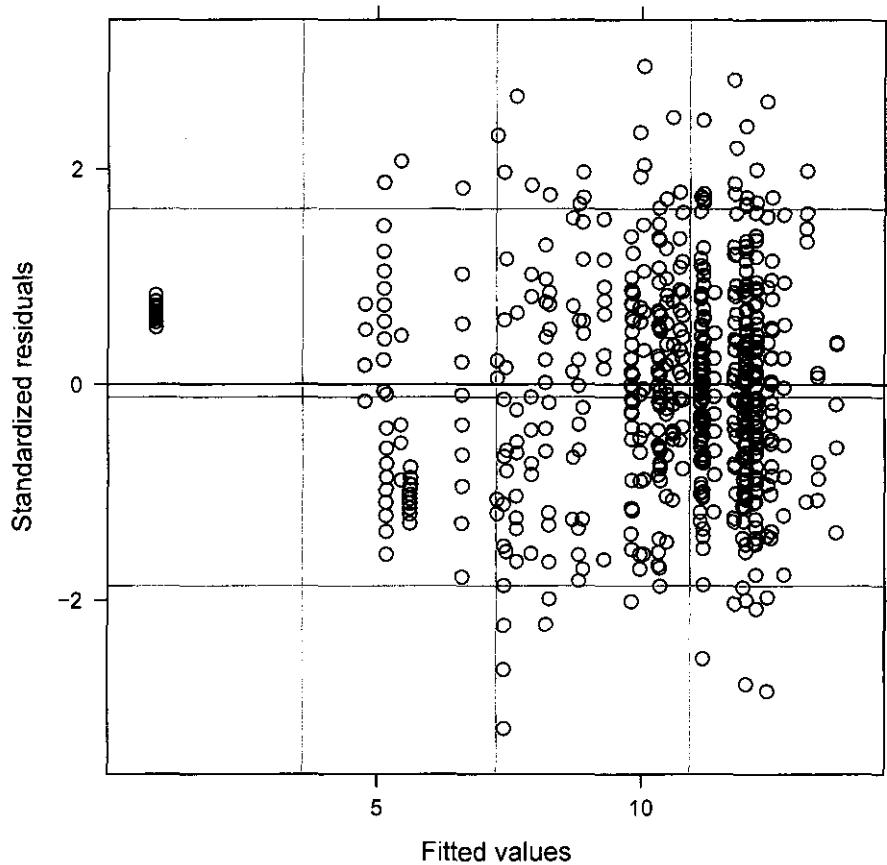
Number of Groups: 3

Diagnostic plots for this model.

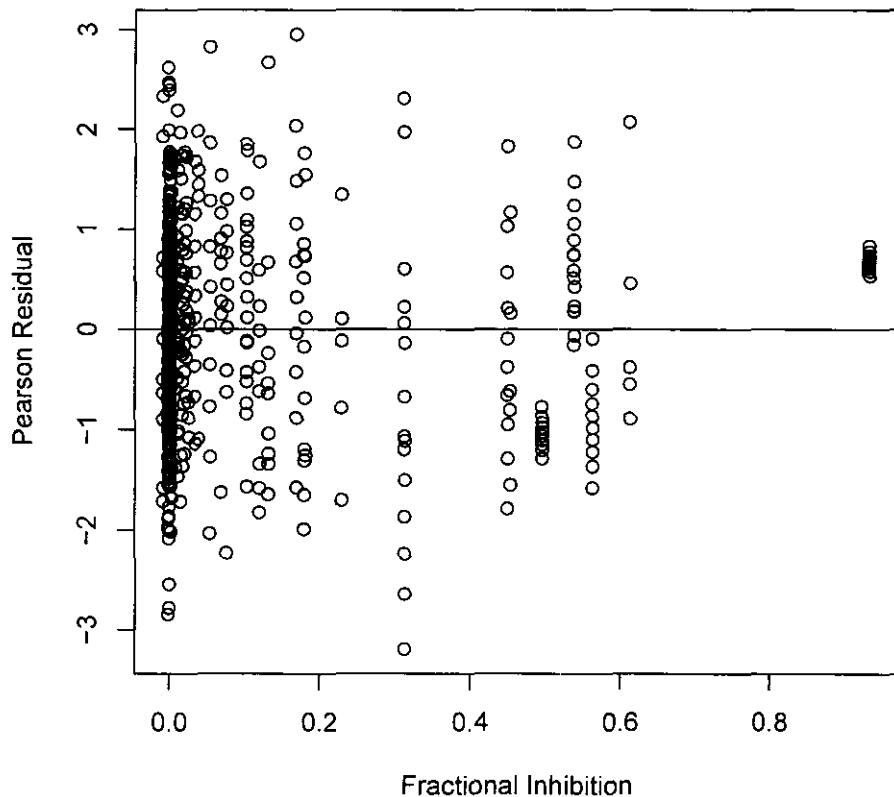
QQ Plot of (Pearson) Scaled Residuals

Normal Q-Q Plot

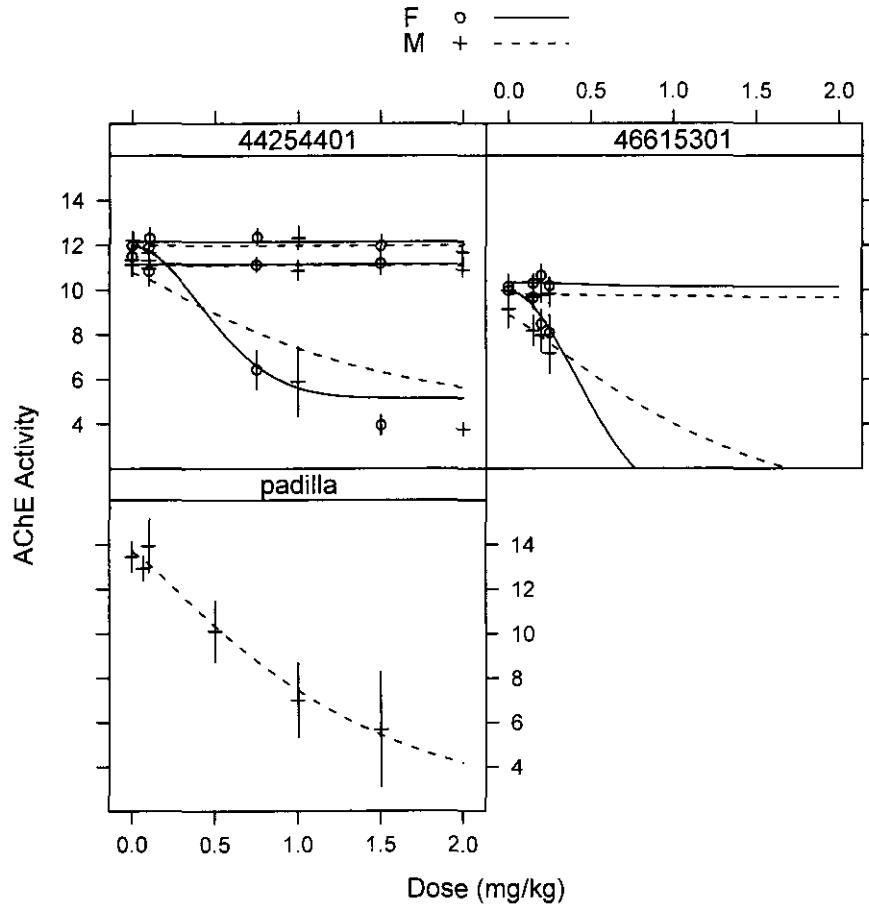
Scaled Residuals versus Fitted Activity Level



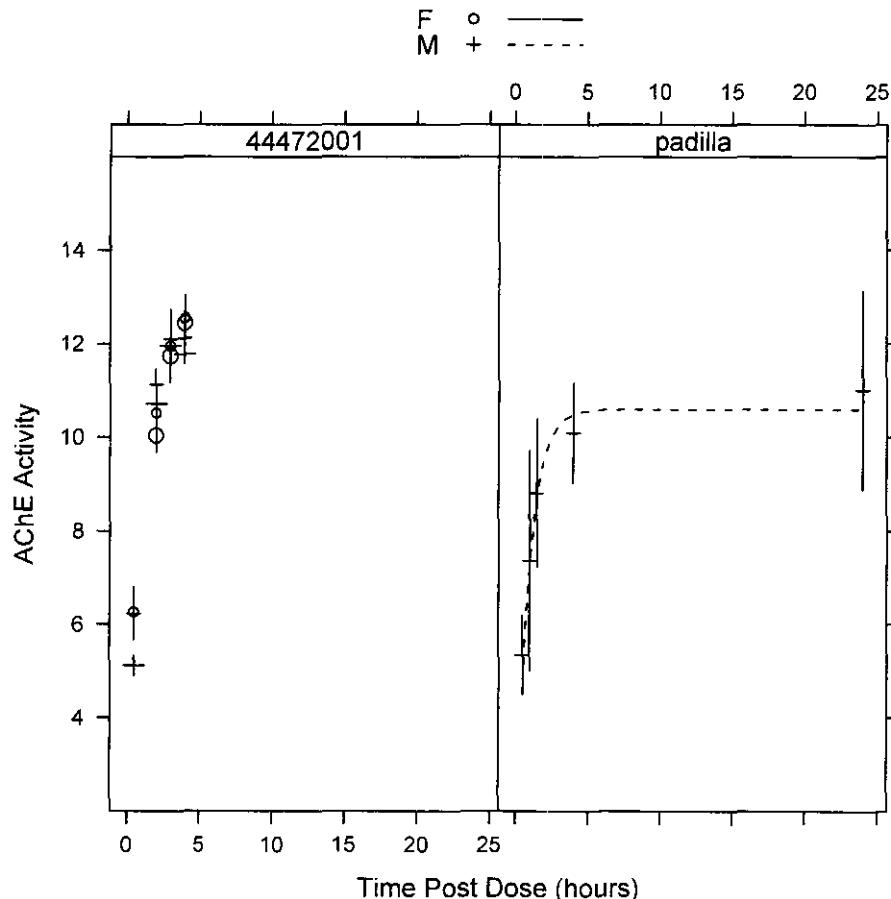
Scaled Residuals versus Fitted Fraction of Inhibition



Next, dose-response and recovery curves with means and 95% confidence intervals from the data.



Timecourses:



In the time course plot for 44472001, the larger symbols correspond to the fitted value for that sex and time point from the model.

4 Analysis of PND11 to Adult Potency Ratios in MRID 46615301

This MRID contain both PND11 and adult dose response information and pnd11 time-course information that can be used to evaluate the ratio of potencies between adults and juveniles.

Extract the data for this subanalysis, and summarize the design used:

```
> dta.ajr <- CleanUp(subset(dta, mrid == "46615301"))
> with(dta.ajr, print(table(dose, tmpstds, age), zero.print = "."))
, , age = adult

      tmpstds
dose   0.5 1 1.5 2 3 4 6
  0     20 . . . . 17 .
  0.075 . . . . . .
  0.1    . . . . . .
  0.125 . . . . . .
  0.15   20 . . . . 20 .
  0.2    20 . . . . 20 .
```

```

0.25   20   .   .   .   20

, , age = pnd11

      tmpstds
dose    0.5  1  1.5  2  3  4  6
0       20  10   .  10   .  10   .
0.075   20   .   .   .   .   .   .
0.1     29  10  10   9  10  10  10
0.125   20   .   .   .   .   .   .
0.15    20   .   .   .   .   .   .
0.2     .   .   .   .   .   .   .
0.25    .   .   .   .   .   .   .

```

Two features stand out here: there is no time course component in the adult dataset (the analysis of the adult data, above, shows that AChE activity has pretty much returned to normal by four hours, so that time point is useless for estimating recovery half life), and there are no controls for three of the seven pnd11 time points. Furthermore, the analysis of the pnd11 control groups reported above shows that they are heterogeneous, with no pattern.

The dose-response component of both age groups was carried out at 0.5 hours after dosing. That value will be the "delta" in the dose-time response model. If we drop the four hour data in the adults, we only need a half-life parameter in the pnd11 animals, as the dose-response data, at 0.5 hour, will be time "0" in the model. Dropping this time group allows us to simultaneously estimate the dose-response and timecourse parameters, simplifying the analysis. There is minimal disadvantage, since AChE activity has substantially recovered by four hours.

```
> dta.ajr <- CleanUp(subset(dta.ajr, (age == "pnd11") | (age == "adult" & tmpstds == 0.5)))
```

Since there is only a single mrid, there are no random effects to consider. We will use generalized non-linear least squares to fit the model, allowing for a power variance model. In addition, given the relatively low levels of inhibition seen in this study, we will not try to estimate the horizontal asymptote parameterized by t_2 .

Get initial values:

| | [,1] | [,2] | [,3] | [,4] | [,5] | [,6] |
|--|-------|------|------|------|------|------|
| CondIndex | 12.78 | 8.93 | 6.80 | 6.41 | 4.43 | 4.35 |
| mu | 0.13 | 0.19 | 0.25 | 0.26 | 0.38 | 0.39 |
| 1A.Controls46615301:F:adult:doseresponse:0.5 | 0.00 | 0.00 | 0.00 | 0.67 | 0.00 | 0.00 |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | 0.00 | 0.00 | 0.56 | 0.00 | 0.00 | 0.00 |
| 1A.Controls46615301:F:pnd11:doseresponse:0.5 | 0.00 | 0.40 | 0.00 | 0.00 | 0.00 | 0.02 |

| | |
|--|-------------------------------|
| 1A.Controls46615301:M:pnd11:doseresponse:0.5 | 0.17 0.00 0.00 0.00 0.11 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:1 | 0.00 0.03 0.00 0.00 0.00 0.06 |
| 1A.Controls46615301:M:pnd11:timecourse:1 | 0.02 0.00 0.00 0.00 0.04 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:missing | 0.00 0.01 0.00 0.00 0.00 0.77 |
| 1A.Controls46615301:M:pnd11:timecourse:missing | 0.00 0.00 0.00 0.00 0.71 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:2 | 0.00 0.00 0.00 0.00 0.00 0.33 |
| 1A.Controls46615301:M:pnd11:timecourse:2 | 0.00 0.00 0.00 0.00 0.21 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:4 | 0.00 0.02 0.00 0.00 0.00 0.32 |
| 1A.Controls46615301:M:pnd11:timecourse:4 | 0.01 0.00 0.00 0.00 0.34 0.00 |
| 1D.ageadult:sexF | 0.00 0.00 0.00 0.98 0.00 0.00 |
| 1D.agepnd11:sexF | 0.00 0.98 0.00 0.00 0.00 0.00 |
| 1D.ageadult:sexM | 0.00 0.00 0.98 0.00 0.00 0.00 |
| 1D.agepnd11:sexM | 0.98 0.00 0.00 0.00 0.00 0.00 |
| lg.ageadult:sexF | 0.00 0.00 0.00 0.81 0.00 0.00 |
| lg.agepnd11:sexF | 0.00 0.86 0.00 0.00 0.00 0.02 |
| lg.ageadult:sexM | 0.00 0.00 0.82 0.00 0.00 0.00 |
| lg.agepnd11:sexM | 0.95 0.00 0.00 0.00 0.01 0.00 |
| 1Tr.sexF | 0.00 0.14 0.00 0.00 0.00 0.80 |
| 1Tr.sexM | 0.06 0.00 0.00 0.00 0.86 0.00 |

Estimates of lg and ID are possibly confounded, but the maximum condition index is probably small enough to go ahead and try a fit. Now, the fit for the control option coded in 'Control2':

```
> Start <- init4$start$beta
> dta.ajr$A.S <- with(dta.ajr, interaction(age, sex, drop = TRUE, sep = ":")) 
> drmod4 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, 1Tr = 1Tr), data = dta.a
+   Controls - 1, 1D ~ age:sex - 1, lg ~ age:sex - 1, 1Tr ~ sex - 1), start = Start, weights = varCom
+   A.S), varPower(value = 1)))
```

Look for simplifications: try to collapse ID, lg, and 1Tr across sex:

```
> anova(drmod4, L = matrix(c(1, -1, 0, 0, 0, 0, -1, 1), nrow = 2, ncol = 4, byrow = TRUE, dimnames = li
+   "1D.ageadult:sexM", "1D.agepnd11:sexF", "1D.agepnd11:sexM")))
```

Denom. DF: 256

F-test for linear combination(s)

| | 1D.ageadult:sexF | 1D.agepnd11:sexF | 1D.ageadult:sexM | 1D.agepnd11:sexM |
|-------|------------------|------------------|------------------|------------------|
| 1 | 1 | 0 | -1 | 0 |
| 2 | 0 | -1 | 0 | 1 |
| numDF | F-value | p-value | | |
| 1 | 2 | 0.2976286 | 0.7428 | |

```
> anova(drmod4, L = matrix(c(1, -1, 0, 0, 0, 0, -1, 1), nrow = 2, ncol = 4, byrow = TRUE, dimnames = li
+   "lg.ageadult:sexM", "lg.agepnd11:sexF", "lg.agepnd11:sexM")))
```

Denom. DF: 256

F-test for linear combination(s)

| | lg.ageadult:sexF | lg.agepnd11:sexF | lg.ageadult:sexM | lg.agepnd11:sexM |
|-------|------------------|------------------|------------------|------------------|
| 1 | 1 | 0 | -1 | 0 |
| 2 | 0 | -1 | 0 | 1 |
| numDF | F-value | p-value | | |
| 1 | 2 | 0.3067143 | 0.7361 | |

```
> anova(drmod4, L = c(1Tr.sexF = 1, 1Tr.sexM = -1))
```

Denom. DF: 256

F-test for linear combination(s)

```

lTr.sexF lTr.sexM
      1      -1
numDF      F-value p-value
1       1 0.005928217  0.9387

```

None of the effects differs between sexes. What is the joint significance of collapsing the remaining effects across sex, simultaneously?

Denom. DF: 256

F-test for linear combination(s)

| | 1D.ageadult:sexF | 1D.agepnd11:sexF | 1D.ageadult:sexM | 1D.agepnd11:sexM | lg.ageadult:sexF | lg.agepnd11:sexF |
|---|------------------|------------------|------------------|------------------|------------------|------------------|
| 1 | 1 | 0 | -1 | 0 | 0 | 0 |
| 2 | 0 | 1 | 0 | -1 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | -1 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | -1 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 |

1Tr.sexM

$$\begin{matrix} 1 & 0 \end{matrix}$$

2 0

3 0

4 0

5 1

```
numDF      F-value   p-value
1          5 0.1363660  0.9838
```

Now fit the simplified model:

```

> ParmS <- coef(drmod4)
> Start <- c(getParmS("lA", ParmS), mean(getParmS("lD.ageadult", ParmS)), mean(getParmS("lD.agepnd11",
+   ParmS)), mean(getParmS("lg.agepnd11", ParmS)), mean(getParmS("lTr", ParmS)))
> drmod5 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data = dta.e,
+   factor(Controls) - 1, lD ~ age - 1, lg ~ age - 1, lTr ~ 1), start = Start, weights = varComb(varL,
+   A.S), varPower(value = 1)))

```

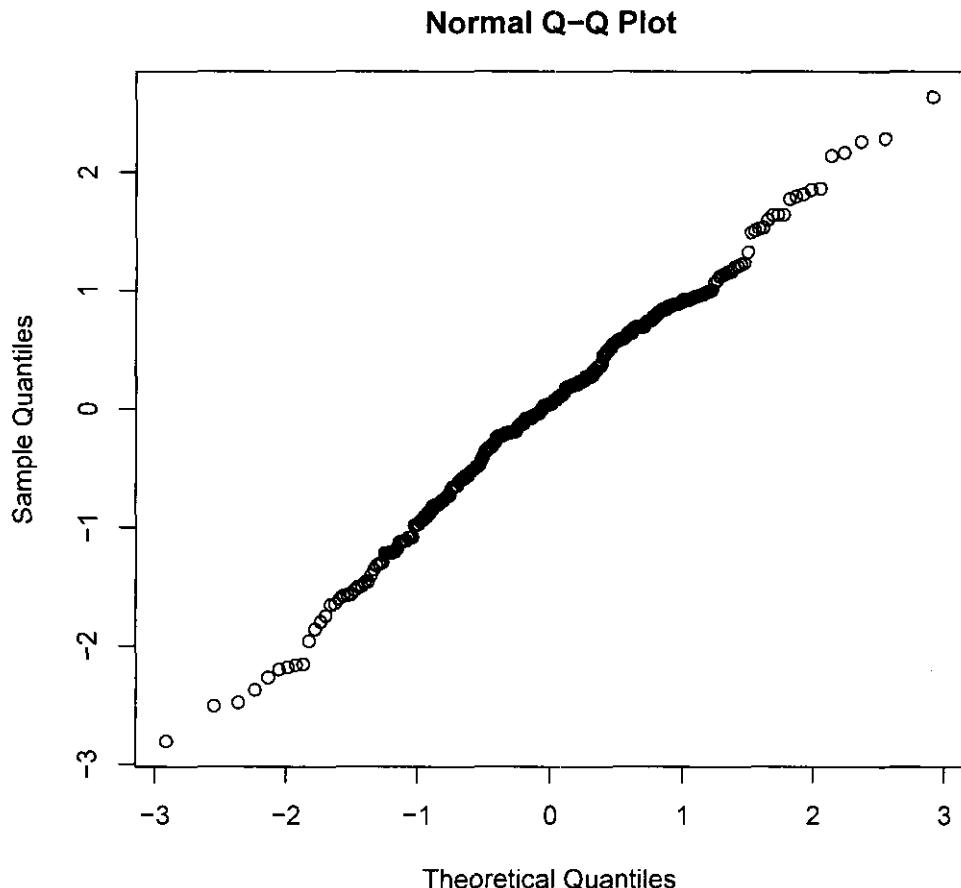
Finally, compare the reduced to the fuller parameterization; look at AIC and BIC, as well as the P-value for the overall comparison. Now, try the alternative control parameterization:

```
> anova(drmmod4, drmod5)
```

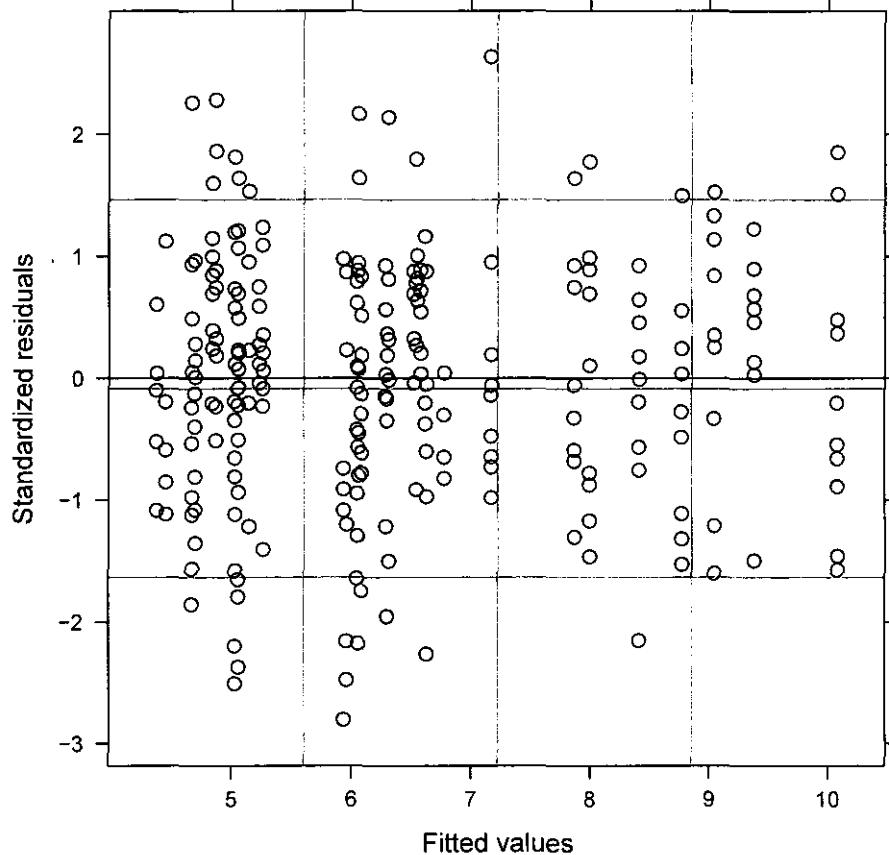
| | Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|--|--------|----|-----|----------|----------|-----------|---------|-----------------|
| | drmod4 | 1 | 27 | 647.7261 | 745.6719 | -296.8630 | | |
| | drmod5 | 2 | 22 | 638.7487 | 718.5564 | -297.3744 | 1 vs 2 | 1.022606 0.9607 |

Note that the P-value is similar to that for the total contrast. The AIC and BIC for the simpler model is smaller. Diagnostic plots for this fit:

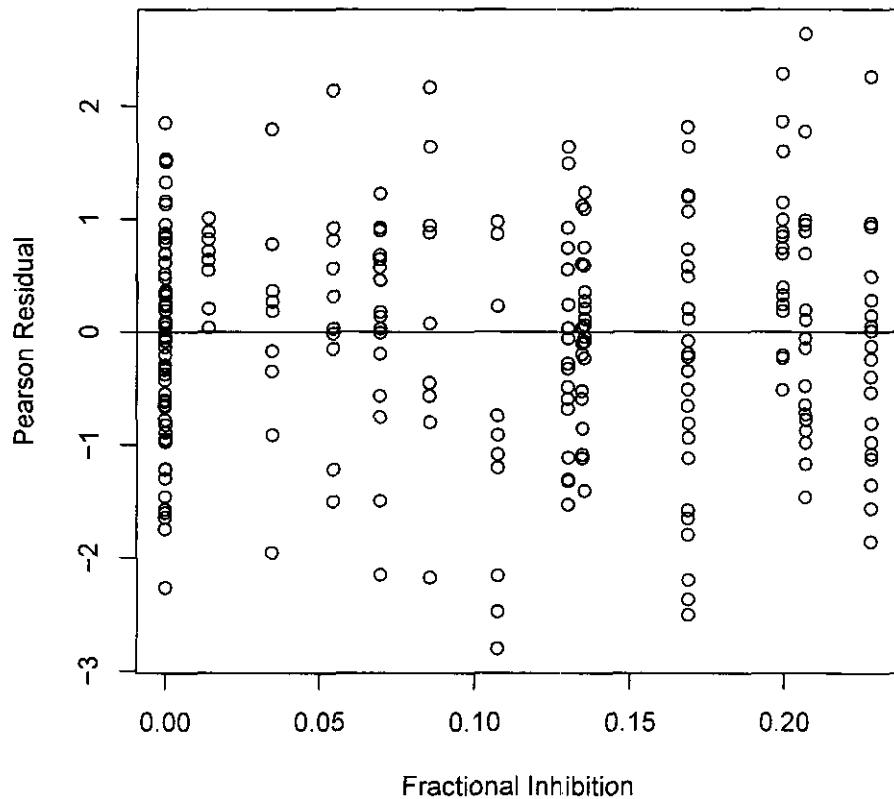
QQ Plot of (Pearson) Scaled Residuals:



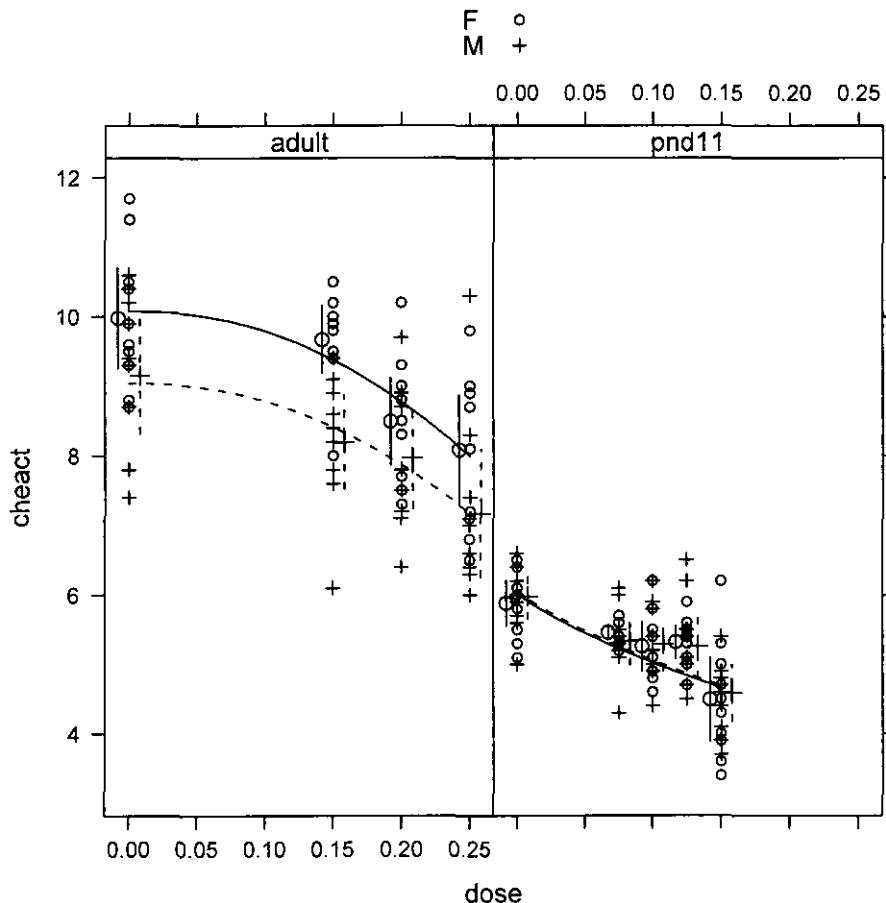
Scaled residuals versus fitted values:



Scaled Residuals versus Predicted Fraction of Inhibition:

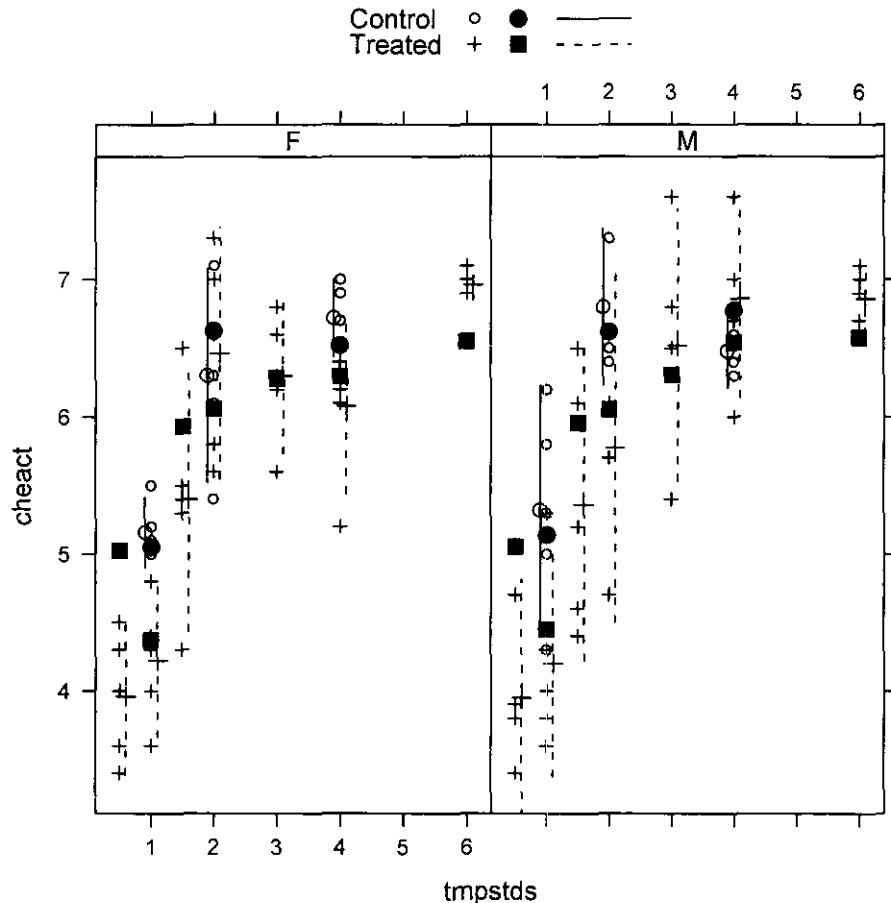


Dose-Response Curves, by age:



Here, the dose-group means for males and females are displaced slightly to the right and left, respectively, of their correct place to make it easier to distinguish the means from the raw data points.

Time Course for pnd11 Animals



Larger, solid symbols represent fitted values from the model. Confidence intervals are 95% confidence intervals for the means.

Two values of interest from this model are the ratio of the adult to the pnd11 BMDs, and the pnd11 recovery half-life. The ratio is conveniently calculated by exponentiating the difference between the log BMDs (ID) for each age group. Confidence intervals are calculated by calculating the standard error for the linear contrast of the two log BMDs, and exponentiating the approximate normal-theory confidence interval for the difference of the log BMDs. This is all carried out by the code below:

```

> cov <- drmod5$varBeta
> Cn <- coef(drmod5)
> Cn[] <- 0
> Cn["1D.ageadult"] <- 1
> Cn["1D.agepnd11"] <- -1
> lpotrat <- Cn %*% coef(drmod5)
> sepotrat <- sqrt(Cn %*% cov %*% Cn)
> potrat <- exp(lpotrat)
> CIpotrat <- exp(lpotrat + qnorm(c(0.025, 0.975)) * sepotrat)

> tTab.j <- summary(drmod5)$tTable
> Ints.j <- intervals(drmod5, which = "coef")$coef
> Ints90.j <- intervals(drmod5, which = "coef", level = 0.9)$coef
> summary(drmod5)

```

Generalized nonlinear least squares fit
 Model: cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
 Data: dta.ajr
 AIC BIC logLik
 638.7487 718.5564 -297.3744

Combination of variance functions:

Structure: Different standard deviations per stratum

Formula: ~1 | A.S

Parameter estimates:

| | | | |
|-----------|-----------|-----------|-----------|
| pnd11:M | pnd11:F | adult:M | adult:F |
| 1.0000000 | 0.9246197 | 2.1396792 | 1.9661641 |

Structure: Power of variance covariate

Formula: ~fitted(.)

Parameter estimates:

| | |
|------------|--|
| power | |
| -0.6516147 | |

Coefficients:

| | Value | Std.Error | t-value | p-value |
|--|------------|-----------|-----------|---------|
| lA.factor(Controls)46615301:F:adult:doseresponse:0.5 | 2.3104536 | 0.0237998 | 97.07871 | 0.0000 |
| lA.factor(Controls)46615301:M:adult:doseresponse:0.5 | 2.2017454 | 0.0273614 | 80.46916 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | 1.7992474 | 0.0238324 | 75.49592 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | 1.8052676 | 0.0246671 | 73.18516 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:1 | 1.6196965 | 0.0456083 | 35.51320 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:1 | 1.6373380 | 0.0478433 | 34.22292 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:missing | 1.8939551 | 0.0320453 | 59.10243 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:missing | 1.8979500 | 0.0333079 | 56.98189 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:2 | 1.8910730 | 0.0300951 | 62.83650 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:2 | 1.8900188 | 0.0330061 | 57.26273 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:4 | 1.8751061 | 0.0297793 | 62.96672 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:4 | 1.9132403 | 0.0301674 | 63.42081 | 0.0000 |
| lD.ageadult | -1.7322614 | 0.1247316 | -13.88791 | 0.0000 |
| lD.agepnd11 | -2.9783984 | 0.3677169 | -8.09971 | 0.0000 |
| lg.ageadult | 0.8242066 | 0.3286712 | 2.50769 | 0.0128 |
| lg.agepnd11 | -0.1835878 | 0.3795337 | -0.48372 | 0.6290 |
| lTr | 0.4272624 | 0.4681774 | 0.91261 | 0.3623 |

Correlation:

| | | |
|--|--------------------|------------|
| lA.(C)46615301:F:: | lA.(C)46615301:M:: | lA.(C)4661 |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | 0.468 | |
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:missing | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:missing | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | 0.000 | 0.000 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | 0.000 | 0.000 |
| lD.ageadult | -0.695 | -0.605 |
| lD.agepnd11 | 0.000 | 0.000 |
| lg.ageadult | -0.450 | -0.392 |

| | | | |
|--|------------------------|--------|--------|
| lg.agepnd11 | 0.000 | 0.000 | -0.223 |
| lTr | 0.000 | 0.000 | -0.254 |
| 1A.(C)46615301:F:11::1 | 1A.(C)46615301:M:11::1 | 1A. | |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | 0.028 | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:missing | 0.085 | 0.081 | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:missing | 0.082 | 0.078 | C |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | 0.053 | 0.050 | C |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | 0.042 | 0.040 | C |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | 0.042 | 0.040 | C |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | 0.041 | 0.039 | C |
| 1D.ageadult | 0.000 | 0.000 | C |
| 1D.agepnd11 | -0.091 | -0.087 | C |
| lg.ageadult | 0.000 | 0.000 | C |
| lg.agepnd11 | -0.057 | -0.054 | C |
| lTr | 0.080 | 0.076 | C |
| 1A.(C)46615301:F:11::2 | 1A.(C)46615301:M:11::2 | 1A. | |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:missing | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:missing | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | 0.124 | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | 0.153 | 0.122 | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | 0.152 | 0.121 | C |
| 1D.ageadult | 0.000 | 0.000 | C |
| 1D.agepnd11 | -0.012 | -0.010 | C |
| lg.ageadult | 0.000 | 0.000 | C |
| lg.agepnd11 | -0.008 | -0.006 | C |
| lTr | 0.362 | 0.289 | C |
| 1D.g11 | lg.gdl | lg.g11 | |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:missing | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:missing | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | | | |
| 1D.ageadult | | | |
| 1D.agepnd11 | | | |
| lg.ageadult | 0.000 | | |
| lg.agepnd11 | 0.920 | 0.000 | |
| lTr | 0.285 | 0.000 | 0.178 |

Standardized residuals:

| Min | Q1 | Med | Q3 | Max |
|-------------|-------------|------------|------------|------------|
| -2.80494866 | -0.60064345 | 0.04186788 | 0.69404589 | 2.63088771 |

Residual standard error: 2.007197

Degrees of freedom: 278 total; 261 residual

5 Summary

The critical estimates from this analysis are listed below. They are printed with greater than usual precision, in case they are to be used in further computation. For reporting, round to two or three significant digits. BMD has units mg/kg, and times are in hours.

species RAT

mrid [1] "44254401" "44472001" "padilla" "46615301"

Adult 1D (standard error) -1.69219560519953 (0.106198845210994)

Adult BMD (95% CI) 0.184114836396363 (0.150069033707590, 0.225884528898284)

Adult BMDL, the one-sided lower 95% CL 0.155096996177245

Results from the comparative ChE study (MRID 46615301)

PND 11 1D (standard error) -2.97839837947599 (0.367716890965807)

PND11 BMD (95% CI) 0.0508742498914749 (0.0246625897276515, 0.104943938596942)

PND11 BMDL, the one-sided lower 95% CL 0.0277257600798766

Adult 1D (standard error) -1.73226143163045 (0.124731606035147)

Adult BMD (95% CI) 0.176883946378769 (0.138363668791, 0.226128222530642)

Adult BMDL, the one-sided lower 95% CL 0.143968971097489

Ratio of Adult to PND11 BMD (95% CI) 3.47688559057084 (1.62432284841536, 7.44232183996708)

Adult lTr (standard error) :

| Value | Std.Error |
|-------------|------------|
| -0.48510375 | 0.06115505 |

Adult Recovery Half-life (95% CI) :

| lower | est. | upper |
|-----------|-----------|-----------|
| 0.5472523 | 0.6156333 | 0.6925588 |

PND11 Recovery Half-Life (95% CI) 1.53305493834278 (0.609800586281015, 3.85414100421038)

Save everything:

```
> save.image(file = "RatBrainDR.RData")
```

Save the results for incorporating into a database:

```
> oxamyl.oral.brain <- list(mrid = levels(dta$mrid), species = "RAT", BMDs = list(adult = list(combined  
+   "Value"], 1D.se = tTab.a["1D", "Std.Error"], BMD = exp(Ints.a["1D", "est."]), BMD.CI = exp(Ints.a  
+   "upper"))], BMDL = exp(Ints90.a["1D", "lower"])), pnd11 = list(combined = list(1D = tTab.j["1D.a  
+   1D.se = tTab.j["1D.agepnd11", "Std.Error"], BMD = exp(Ints.j["1D.agepnd11", "est."]), BMD.CI = ex  
+   c("lower", "upper"))], BMDL = exp(Ints90.j["1D.agepnd11", "lower"]))), HalfLives = list(adul  
+   rownames(tTab.a), "Value"], lTr.se = tTab.a[grep("^lTr", rownames(tTab.a)), "Std.Error"], Tr = e  
+   rownames(Ints.a), "est."]), Tr.CI = exp(Ints.a[c("lower", "upper"))], pnd11 = list(lTr = tTab.j  
+   lTr.se = tTab.j["lTr", "Std.Error"], Tr = exp(Ints.j["lTr", "est."]), Tr.CI = exp(Ints.j["lTr", "c  
> save(oxamyl.oral.brain, file = file.path("../", "..", "O1Summaries", "oxamyl.oral.brain.RData"))
```

APPENDIX B

Oxamyl: AChE Rat RBC Summary

Dose-Time Response Modeling of Rat RBC AChE Activity: Oxamyl Gavage Dosing

September 30, 2009

1 Preamble

Here is some code to set up the analysis: loading required libraries and datasets, and defining some functions.

First, CarbamateData loads the full dataset for this risk assessment, and causes the library DRUtils to be loaded.

```
> library(CarbamateData)
```

Set up lattice to use B&W instead of color:

```
> library(lattice)
> ltheme <- canonical.theme(color = FALSE)
> ltheme$strip.background$col <- "transparent"
> lattice.options(default.theme = ltheme)
```

Use package Hmisc for some formatting support. All the rat gavage data for this analysis are in AggData and PadillaData. The following code prints out documentation for the datasets in use:

```
> printDataDoc(AggData)
```

```
-----
Data set: AggData

Dataset creation date: Mon May 05 12:20:50 2008
Script name: C:/EmpiricalDoseResponses/Data/getdata.R
Script last modified: 2008-05-05 12:18:40
sysname: Windows
release: XP
version: build 2600, Service Pack 2
nodename: L2032JPVILLANU
machine: x86
login: pvillanu
user: pvillanu
```

```
> printDataDoc(PadillaData)
```

```
-----
Data set: PadillaData

Dataset creation date: Mon May 05 12:20:58 2008
Script name: C:/EmpiricalDoseResponses/Data/getdata.R
Script last modified: 2008-05-05 12:18:40
```

```

sysname: Windows
release: XP
version: build 2600, Service Pack 2
nodename: L2032JPVILLANU
machine: x86
login: pvillanu
user: pvillanu
-----
```

The following function turns out to be quite useful on subsetted dataframes. It just eliminates unused levels of all factors in the data frame:

```

> CleanUp <- function(x) {
+   for (nm in names(x)) {
+     if (is.factor(x[, nm]))
+       x[, nm] <- factor(x[, nm])
+   }
+   x
+ }
```

To get starting values, we often have to extract values from a previously fit model. The following function simplifies that. The argument what is a regular expression:

```

> getParms <- function(what, Par) {
+   Par[grep(what, names(Par))]
+ }
```

This script is for modeling the dose-time response for rat red blood cells via gavage dosing. It includes acute and subchronic studies.

All the data used for this DR model are in AggData and in PadillaData. The carbaryl data need to be extracted from both data sets, then several variables ($n = 1$, $sd = 0$, $tmonstdy = 1$, $mrid = "Padilla"$, $cheact = RBC.R$) added to the Padilla dataset.

Now, set up the analysis dataset.

```

> dta <- CleanUp(subset(AggData, chemical %in% "OXAMYL" & species %in% "RAT" & dsmtd %in% "GAVAGE" & sc
+   !is.na(cheact) & (n == 1 | !is.na(sd)), select = c("cheact", "sd", "n", "dose", "tmonstdy", "tmps
+   "species")))
> tdt <- with(dta, PhonyDF(dose, n, cheact, sd, "dose", "cheact", Avals = dta[, c("tmpstds", "sex", "n
> tdt$age <- factor(rep("adult", nrow(tdt)), levels = c("adult", "pnd11"))
> tdt$type <- factor(c(`44254401` = "doseresponse", `44420301` = "doseresponse", `44472001` = "timecor
> tdt$cheact <- tdt$cheact/5
> Pdta <- subset(PadillaData, chemical %in% "oxamyl", select = c("dose", "RBC.R", "TMPSTDS"))
> names(Pdta) <- c("dose", "cheact", "tmpstds")
> Pdta$tmonstdy <- rep(1, nrow(Pdta))
> Pdta$n <- rep(1, nrow(Pdta))
> Pdta$sd <- rep(0, nrow(Pdta))
> Pdta$sex <- factor(rep("M", nrow(Pdta)))
> Pdta$age <- factor(rep("adult", nrow(Pdta)), levels = c("adult", "pnd11"))
> Pdta$type <- factor(ifelse(abs(Pdta$tmpstds - 2/3) < 0.001, "doseresponse", "timecourse"))
> Pdta$mrid <- factor(rep("Padilla", nrow(Pdta)))
> Pdta$species <- factor(rep(levels(dta$species)[1], nrow(Pdta)))
> dta2 <- CleanUp(subset(newdata, chemical %in% "Oxamyl", select = c("dose", "rbc", "time", "age", "sex
> names(dta2) <- c("dose", "cheact", "tmpstds", "age", "sex", "mrid")
> dta2$tmpstds <- dta2$tmpstds/60
> dta2$age <- factor(ifelse(dta2$age > 40, "adult", "pnd11"))
> dta2$type <- factor(c(rep("timecourse", 100), rep("doseresponse", nrow(dta2) - 100)))
```

```
> dta2 <- dta2[!is.na(dta2$cheact), ]
> dta2$cheact <- dta2$cheact/5
> dta <- rbind(tdta, Pdta[, names(tdta)], dta2[, names(tdta)])
```

Summary of the relevant variables in this dataset:

```
> by(dta, dta$mrid, summary)
```

dta\$mrid: 44254401

| dose | cheact | tmpstds | sex | mrid | age | type |
|----------------|----------------|----------------|-------|--------------|-----------|------------------|
| Min. :0.0000 | Min. : 82.58 | Min. : -1.00 | F:160 | 44254401:319 | adult:319 | doseresponse:319 |
| 1st Qu.:0.0500 | 1st Qu.:288.97 | 1st Qu.: 0.00 | M:159 | 44472001: 0 | pnd11: 0 | timecourse : 0 |
| Median :0.1000 | Median :351.03 | Median : 1.00 | | Padilla : 0 | | |
| Mean :0.6771 | Mean :347.83 | Mean : 96.23 | | 46615301: 0 | | |
| 3rd Qu.:1.0000 | 3rd Qu.:415.09 | 3rd Qu.:192.00 | | | | |
| Max. :2.0000 | Max. :665.07 | Max. :360.00 | | | | |

dta\$mrid: 44472001

| dose | cheact | tmpstds | sex | mrid | age | type |
|-------------|----------------|---------------|------|--------------|-----------|-----------------|
| Min. :0.0 | Min. : 98.08 | Min. :0.500 | F:80 | 44254401: 0 | adult:160 | doseresponse: 0 |
| 1st Qu.:0.0 | 1st Qu.:305.50 | 1st Qu.:1.625 | M:80 | 44472001:160 | pnd11: 0 | timecourse :160 |
| Median :0.5 | Median :371.39 | Median :2.500 | | Padilla : 0 | | |
| Mean :0.5 | Mean :363.98 | Mean :2.375 | | 46615301: 0 | | |
| 3rd Qu.:1.0 | 3rd Qu.:432.13 | 3rd Qu.:3.250 | | | | |
| Max. :1.0 | Max. :593.47 | Max. :4.000 | | | | |

dta\$mrid: Padilla

| dose | cheact | tmpstds | sex | mrid | age | type |
|----------------|----------------|-----------------|------|-------------|----------|-----------------|
| Min. :0.0000 | Min. : 32.76 | Min. : 0.5000 | F: 0 | 44254401: 0 | adult:59 | doseresponse:30 |
| 1st Qu.:0.0833 | 1st Qu.:113.44 | 1st Qu.: 0.6667 | M:59 | 44472001: 0 | pnd11: 0 | timecourse :29 |
| Median :1.0000 | Median :267.32 | Median : 0.6667 | | Padilla :59 | | |
| Mean :0.6751 | Mean :259.49 | Mean : 3.0847 | | 46615301: 0 | | |
| 3rd Qu.:1.0000 | 3rd Qu.:409.32 | 3rd Qu.: 1.5000 | | | | |
| Max. :1.5000 | Max. :563.89 | Max. :24.0000 | | | | |

dta\$mrid: 46615301

| dose | cheact | tmpstds | sex | mrid | age | type |
|----------------|---------------|---------------|-------|--------------|-----------|------------------|
| Min. :0.0000 | Min. :144.0 | Min. :0.500 | F:174 | 44254401: 0 | adult:157 | doseresponse:251 |
| 1st Qu.:0.0750 | 1st Qu.:344.0 | 1st Qu.:0.500 | M:170 | 44472001: 0 | pnd11:187 | timecourse : 93 |
| Median :0.1000 | Median :448.0 | Median :0.500 | | Padilla : 0 | | |
| Mean :0.1137 | Mean :442.5 | Mean : 1.821 | | 46615301:344 | | |
| 3rd Qu.:0.1500 | 3rd Qu.:552.0 | 3rd Qu.:4.000 | | | | |
| Max. :0.2500 | Max. :780.0 | Max. :6.000 | | | | |

```
> unique(subset(dta, select = c("mrid", "tmpstds")))
```

| mrid | tmpstds |
|--------------|-------------|
| 1 44254401 | -1.0000000 |
| 41 44254401 | 1.0000000 |
| 81 44254401 | 24.0000000 |
| 120 44254401 | 360.0000000 |
| 320 44472001 | 0.5000000 |
| 330 44472001 | 2.0000000 |
| 340 44472001 | 3.0000000 |
| 350 44472001 | 4.0000000 |

```
3210 Padilla 0.6666667
3711 Padilla 0.5000000
3811 Padilla 1.0000000
3911 Padilla 1.5000000
4011 Padilla 4.0000000
4111 Padilla 24.0000000
1290 46615301 1.0000000
1295 46615301 2.0000000
1301 46615301 4.0000000
1305 46615301 0.5000000
1316 46615301 1.5000000
1325 46615301 3.0000000
1335 46615301 6.0000000

> by(dta, dta$mrid, function(x) with(x, table(dose, tmpstds)))

dta$mrid: 44254401
    tmpstds
dose   -1  1 24 360
  0   20 20 20 20
  0.1 20 20 20 20
  0.75 10 10 10 10
  1   10 10 10 10
  1.5 10 10 10 10
  2   10 10  9 10
-----
dta$mrid: 44472001
    tmpstds
dose 0.5  2  3  4
  0   20 20 20 20
  1   20 20 20 20
-----
dta$mrid: Padilla
    tmpstds
dose      0.5 0.6666666666666667 1 1.5 4 24
  0       1           5 1   1 1   1
  0.0666  0           5 0   0 0   0
  0.1     0           5 0   0 0   0
  0.5     0           5 0   0 0   0
  1       5           5 5   5 5   4
  1.5     0           5 0   0 0   0
-----
dta$mrid: 46615301
    tmpstds
dose   0.5  1 1.5  2  3  4   6
  0     38 10  0 10  0 25  0
  0.075 19  0   0  0  0  0  0
  0.1   26 10  9  9 10 10  9
  0.125 19  0   0  0  0  0  0
  0.15  40  0   0  0  0 20  0
  0.2   20  0   0  0  0 20  0
  0.25  20  0   0  0  0 20  0
```

Padilla's data are from an acute study, with multiple doses at one time point, and multiple timepoints for 1 mg/kg. Mrids 44254401 and 44472001 are acute studies. Also, in 44254401, only the 1 hour time point is likely

to be useful, since AChE activity should be at background by the next time point, 24 hours. Note the negative time in 44254401. This indicates pre-study baseline values (dose == 0). Set up a new dose variable, dose2 that is 0 when tmpstds is negative. Since this study does not involve repeated measures, these extra groups are only useful for estimating variance.

```
> dta$dose2 <- ifelse(dta$tmpstds < 0, 0, dta$dose)
```

Create some new factors, for splitting up the background parameters and allowing groups to have different variances.

```
> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE, sep = ":"))  
> dta$mridXsexXtmpstds <- with(dta, interaction(mrid, sex, tmpstds, drop = TRUE, sep = ":"))
```

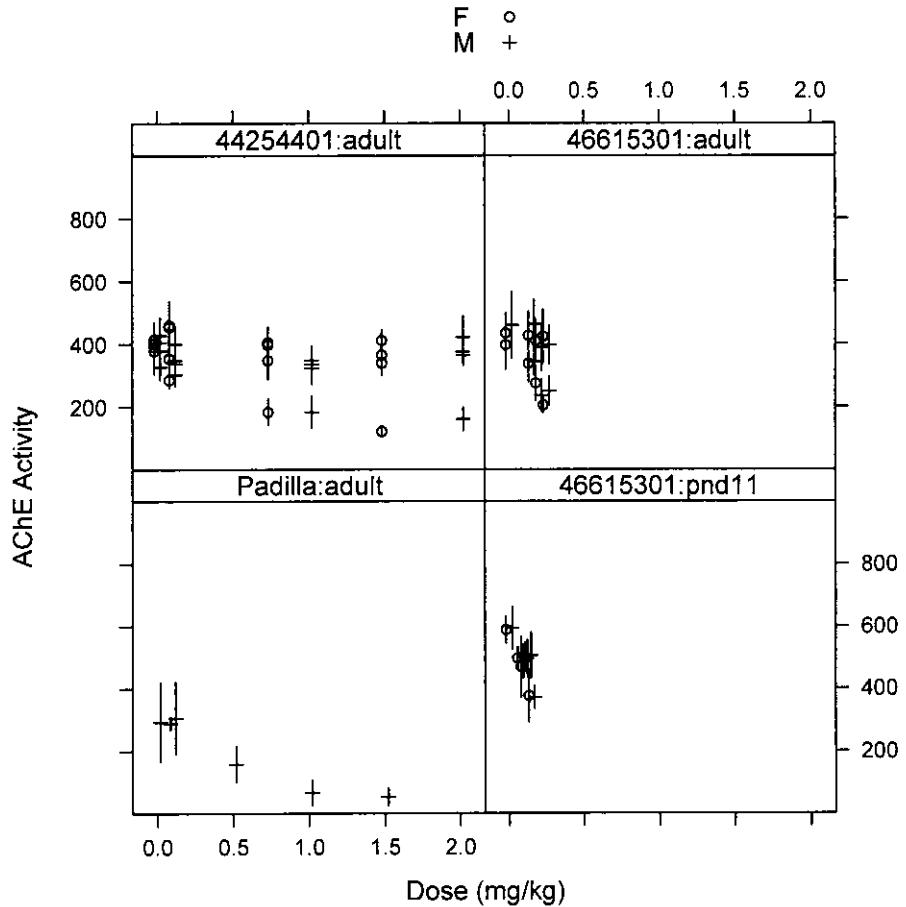
We only have useful time course data at a single dose, 1 mg/kg, in both the Padilla study and in 44472001. Thus, only a single value for 1Tr will be estimated.

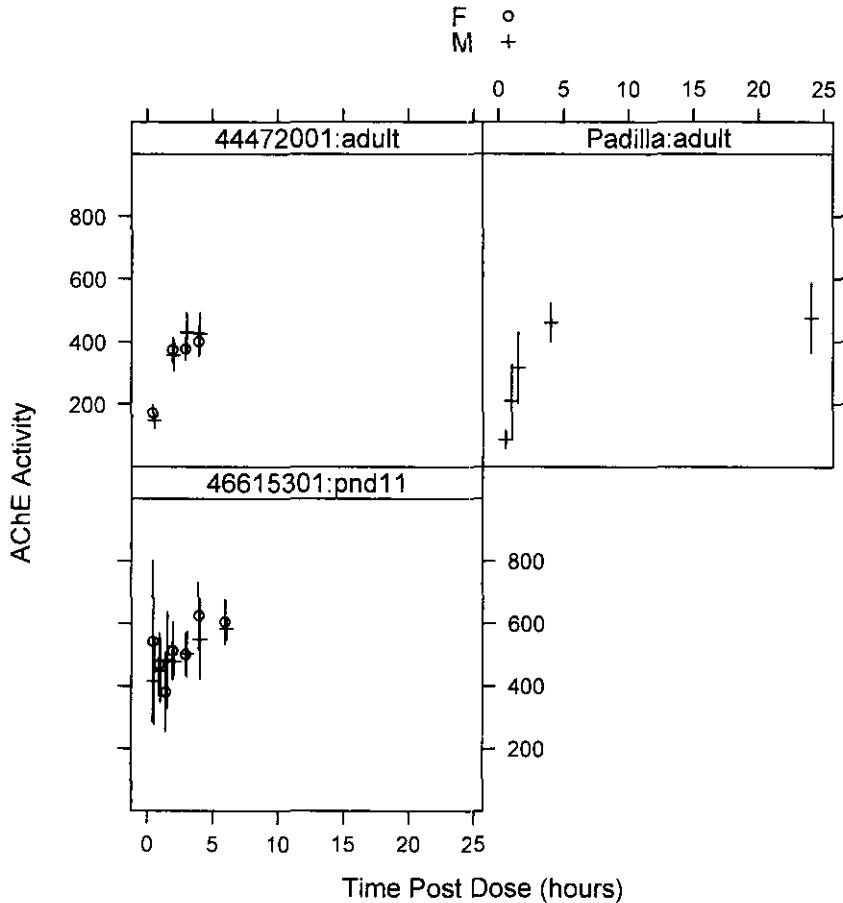
2 Dose-Response Modeling

2.1 A Quick Look at the Data

```
> dta$cells <- with(dta, interaction(mrid, age, sex, dose, tmpstds, type, drop = TRUE, sep = ":"))  
> tmp <- tapply(dta$cheact, dta$cells, function(x) c(mean(x), sd(x), length(x)))  
> nm <- names(tmp)  
> tmp <- matrix(unlist(tmp), ncol = 3, byrow = TRUE)  
> rownames(tmp) <- nm  
> nmmx <- matrix(unlist(strsplit(nm, ":")), ncol = 6, byrow = TRUE)  
> dta.summ <- data.frame(che = tmp[, 1], che.lower = ifelse(tmp[, 3] > 1, tmp[, 1] + qt(0.025, tmp[, 3]  
+ 3]), NA), che.upper = ifelse(tmp[, 3] > 1, tmp[, 1] + qt(0.975, tmp[, 3] - 1) * tmp[, 2]/sqrt(tmp[,  
+ 1])), age = factor(nmmx[, 2]), sex = factor(nmmx[, 3]), dose = as.numeric(nmmx[, 4]), tmpstds = as.  
+ 5]), type = factor(nmmx[, 6]))
```

Dose-Response





Time Course

Apparently, the response is already increasing at the 30 minute time point, so the time to peak effect is not greater than 30 minutes for RBC AChE inhibition.

2.2 strategy

There are two sets of goals for this analysis. For all the adult data, we need an estimate for the dose that would result in 10% RBC AChE inhibition (the benchmark dose, BMD), as well as an estimate of the half-life of recovery from peak inhibition. For the study that contains both adult and pnd11 animals, we want an estimate of age-specific BMD, and the ratio of adult to pnd11 BMD, and the age-specific half-life. Thus, two analyses are required: one of all the adult data, and the other of all the data from MRID 46615301.

Each analysis will proceed in a similar fashion. First, how do we handle the controls? There are typically controls at each time point for studies of recovery. If the control values are homogeneous, then it will simplify the analysis to fit a common control value across all time points for each study. If the control values are heterogeneous, then we assume that the concurrent control is the appropriate point of comparison for the activity in a dose group, so a factor needs to be set up to allow control values to vary across time points. The EPA study has a single animal per time point in the time-course study, so the critical questions for that study will be:

- is there a time-related trend among the controls?
- is the variance among the time-course controls significantly greater than that among the dose-response controls?
- does the mean time-course control value differ significantly from the mean dose-response control value.

In 44472001, there is a control group for each time. For this study the questions will be, for each sex: do the two time-course controls differ?

In the pnd11 animals of 46615301, there are concurrent controls for only some of the time points. Thus, in addition to determining whether the controls are heterogeneous across time, if the answer is "yes", then we need to determine how to set a control level for each time point.

In the registrant-submitted studies, we will maintain differences between sex and age, at the least.

The remaining dose-response parameters are initially allowed to vary among MRID and sex (and age, when appropriate), to the extent possible for the design (in particular, the recovery half-life can only be estimated in studies where there is a *recovery component*). Once a model is fit, Wald type tests are used to collapse the initial richly parameterized model to a simpler one; for example, if the data do not support allowing *lg* to vary among studies or sexes, fitting a simpler parameterization.

The dose-response parameters, *ID*, *lg*, and *tz* may not be estimable with the data at hand. In particular, it is generally not possible to estimate *tz*, unless doses are so great that the response has reached its asymptotic value. In the course of getting initial values for these parameters, if it is clear that *tz* cannot be estimated, it is fixed at -10, which sets the maximum possible inhibition level to be nearly 100%.

2.3 How Heterogeneous are the Time Course Controls?

The EPA dataset has just one animal per time point in the time course control group. We can do tests there to determine whether there is any additional variability among times: regression of response on time among the controls to look for trends, and comparison of the variance among times to the variance among the control animals from the dose-response portion of the study. We do these tests here. First, regression of the responses on time:

```
> print(summary(tmp <- lm(cheact ~ tmpstds, data = subset(dta, mrid == "Padilla" & dose == 0 & type == "timecourse")))

Call:
lm(formula = cheact ~ tmpstds, data = subset(dta, mrid == "Padilla" &
dose == 0 & type == "timecourse"))

Residuals:
 3711   3811   3911   4011   4111
-1.623  16.126 -9.815 -5.596  0.908

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 422.9653     6.2051  68.164 6.96e-06 ***
tmpstds      2.9544     0.5686   5.196   0.0138 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 11.42 on 3 degrees of freedom
Multiple R-squared:  0.9,          Adjusted R-squared:  0.8667
F-statistic:  27 on 1 and 3 DF,  p-value: 0.01385
```

The test for trend is the significance of the coefficient for *tmpstds*. The *P*-value is 0.0138, so there is evidence for a trend. However, the change in magnitude is small (and the regression depends strongly on a single influential point). Allowing for a linear trend in the controls for this group would make the whole analysis more complex, so we fit a separate control value for the dose-response study in the Padilla dataset.

Next, how heterogeneous are the controls in 44472001? We test for both trend and heterogeneity:

```
> with(subset(dta, mrid == "44472001" & dose == 0), {
+   print(summary(lm(cheact ~ sex + tmpstds + tmpstds:sex)))
+   print(summary(lm(cheact ~ sex + tmpstds)))
+   out1 <- lm(cheact ~ sex * factor(tmpstds))
```

```

+      out2 <- lm(cheact ~ sex + factor(tmpstds))
+      print(anova(out1, out2, test = "F"))
+ })

Call:
lm(formula = cheact ~ sex + tmpstds + tmpstds:sex)

Residuals:
    Min      1Q   Median      3Q      Max 
-136.898 -53.049  -5.139   43.359  188.734 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept)  439.925    23.586  18.652 < 2e-16 ***
sexM        -133.525    33.355  -4.003 0.000144 ***  
tmpstds     -20.516     8.722  -2.352 0.021254 *  
sexM:tmpstds  57.316    12.335   4.647 1.39e-05 *** 
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 71.33 on 76 degrees of freedom
Multiple R-squared:  0.2351,    Adjusted R-squared:  0.2049 
F-statistic: 7.787 on 3 and 76 DF,  p-value: 0.0001337

Call:
lm(formula = cheact ~ sex + tmpstds)

Residuals:
    Min      1Q   Median      3Q      Max 
-168.198 -54.547  -4.273   57.563  186.443 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept) 371.863    20.812  17.868 <2e-16 ***
sexM         2.600     17.955   0.145   0.885    
tmpstds      8.142     6.943   1.173   0.245    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 80.3 on 77 degrees of freedom
Multiple R-squared:  0.01781,  Adjusted R-squared:  -0.007703 
F-statistic: 0.698 on 2 and 77 DF,  p-value: 0.5007

Analysis of Variance Table

Model 1: cheact ~ sex * factor(tmpstds)
Model 2: cheact ~ sex + factor(tmpstds)
  Res.Df   RSS Df Sum of Sq    F    Pr(>F)    
1      72 338162                                 
2      75 458953 -3   -120791 8.5728 6.104e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

There is a significant linear trend that differs between the sexes and interaction between time and sex in the variability of the means. For this study, we keep a separate control value for each sex and time.

Adults for 46615301. There is no time course here, but males and females may not differ, and the dose-response was evaluated at 0.5 and 4 hours.

```
> with(subset(dta, mrid == "46615301" & age == "adult" & dose == 0), {
+   print(summary(lm(cheact ~ sex + tmpstds + tmpstds:sex)))
+   print(summary(lm(cheact ~ sex + tmpstds)))
+   out1 <- lm(cheact ~ sex * factor(tmpstds))
+   out2 <- lm(cheact ~ sex + factor(tmpstds))
+   print(anova(out1, out2, test = "F"))
+   print(summary(out2))
+ })
```

Call:

```
lm(formula = cheact ~ sex + tmpstds + tmpstds:sex)
```

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|--------|--------|-------|--------|
| -179.43 | -63.43 | -10.40 | 73.60 | 193.60 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|--------------|----------|------------|---------|--------------|
| (Intercept) | 439.35 | 36.38 | 12.075 | 1.18e-13 *** |
| sexM | 18.90 | 51.54 | 0.367 | 0.716 |
| tmpstds | -10.74 | 12.76 | -0.841 | 0.406 |
| sexM:tmpstds | 11.03 | 18.99 | 0.581 | 0.565 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 S S 1

Residual standard error: 99.9 on 33 degrees of freedom

Multiple R-squared: 0.0694, Adjusted R-squared: -0.0152

F-statistic: 0.8204 on 3 and 33 DF, p-value: 0.492

Call:

```
lm(formula = cheact ~ sex + tmpstds)
```

Residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|---------|--------|--------|---------|
| -185.118 | -53.262 | -9.262 | 64.882 | 184.882 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|--------------|
| (Intercept) | 428.140 | 30.542 | 14.018 | 1.08e-15 *** |
| sexM | 41.856 | 32.760 | 1.278 | 0.210 |
| tmpstds | -5.755 | 9.360 | -0.615 | 0.543 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 S S 1

Residual standard error: 98.92 on 34 degrees of freedom

Multiple R-squared: 0.05989, Adjusted R-squared: 0.00459

F-statistic: 1.083 on 2 and 34 DF, p-value: 0.35

Analysis of Variance Table

```

Model 1: cheact ~ sex * factor(tmpstds)
Model 2: cheact ~ sex + factor(tmpstds)
  Res.Df   RSS Df Sum of Sq    F Pr(>F)
1     33 329333
2     34 332699 -1      -3366 0.3373 0.5654

Call:
lm(formula = cheact ~ sex + factor(tmpstds))

Residuals:
    Min      1Q Median      3Q      Max
-185.118 -53.262 -9.262  64.882 184.882

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 425.26     27.52  15.451 <2e-16 ***
sexM        41.86     32.76   1.278   0.210
factor(tmpstds)4 -20.14     32.76  -0.615   0.543
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1  . 1

```

Residual standard error: 98.92 on 34 degrees of freedom
 Multiple R-squared: 0.05989, Adjusted R-squared: 0.00459
 F-statistic: 1.083 on 2 and 34 DF, p-value: 0.35

All adult control groups in 46615301 are similar enough that we fit a common value for all of them.

Finally, the controls for the pnd11 animals of 46615301. We combine the timecourse and dose-response portions, because the 0.5 hour control timepoint is just in the dose-response portion of the study.

```

> with(subset(dta, mrid == "46615301" & age == "pnd11" & dose == 0), {
+   print(summary(lm(cheact ~ sex + tmpstds + tmpstds:sex)))
+   print(summary(lm(cheact ~ sex + tmpstds)))
+   out1 <- lm(cheact ~ sex * factor(tmpstds))
+   out2 <- lm(cheact ~ sex + factor(tmpstds))
+   print(anova(out1, out2, test = "F"))
+   print(summary(out2))
+ })

```

Call:
`lm(formula = cheact ~ sex + tmpstds + tmpstds:sex)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|--------|--------|-------|--------|
| -199.38 | -50.97 | 21.04 | 45.03 | 185.03 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|--------------|----------|------------|---------|------------|
| (Intercept) | 602.92 | 27.33 | 22.058 | <2e-16 *** |
| sexM | -25.53 | 40.10 | -0.637 | 0.528 |
| tmpstds | -15.95 | 14.00 | -1.139 | 0.261 |
| sexM:tmpstds | 16.45 | 20.10 | 0.818 | 0.418 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 . 1

Residual standard error: 85.72 on 42 degrees of freedom
 Multiple R-squared: 0.03002, Adjusted R-squared: -0.03926
 F-statistic: 0.4333 on 3 and 42 DF, p-value: 0.7302

Call:
`lm(formula = cheact ~ sex + tmpstds)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|--------|--------|-------|--------|
| -178.98 | -50.99 | 22.97 | 50.05 | 189.01 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|-----------|------------|---------|------------|
| (Intercept) | 590.95506 | 23.00299 | 25.690 | <2e-16 *** |
| sexM | -0.09363 | 25.22108 | -0.004 | 0.997 |
| tmpstds | -7.97004 | 10.00689 | -0.796 | 0.430 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 S S 1

Residual standard error: 85.39 on 43 degrees of freedom
 Multiple R-squared: 0.01456, Adjusted R-squared: -0.03127
 F-statistic: 0.3177 on 2 and 43 DF, p-value: 0.7295

Analysis of Variance Table

| Model 1: cheact ~ sex * factor(tmpstds) |
|---|
|---|

| Model 2: cheact ~ sex + factor(tmpstds) | | | | | |
|---|-----|--------|-----------|--------|---------------|
| Res.Df | RSS | Df | Sum of Sq | F | Pr(>F) |
| 1 | 38 | 290453 | | | |
| 2 | 41 | 305801 | -3 | -15348 | 0.6693 0.5761 |

Call:

`lm(formula = cheact ~ sex + factor(tmpstds))`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|--------|--------|-------|--------|
| -172.60 | -49.15 | 16.50 | 49.86 | 208.50 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|------------------|----------|------------|---------|------------|
| (Intercept) | 590.1359 | 23.3045 | 25.323 | <2e-16 *** |
| sexM | 0.1942 | 25.5288 | 0.008 | 0.994 |
| factor(tmpstds)1 | -26.6330 | 34.0916 | -0.781 | 0.439 |
| factor(tmpstds)2 | 3.3670 | 34.0916 | 0.099 | 0.922 |
| factor(tmpstds)4 | -37.7330 | 36.7246 | -1.027 | 0.310 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 S S 1

Residual standard error: 86.36 on 41 degrees of freedom
 Multiple R-squared: 0.03891, Adjusted R-squared: -0.05485
 F-statistic: 0.415 on 4 and 41 DF, p-value: 0.7968

Do the 0.1 mg/kg time course group at 0.5 hour differ from the 0.1 mg/kg dose-response group at 0.5 hour? If not, assign the same control group at that time to both groups:

```
> with(subset(dta, mrid == "46615301" & age == "pnd11" & dose == 0.1), {
+   print(summary(lm(cheact ~ type * sex)))
+   print(summary(lm(cheact ~ type + sex)))
+ })
```

Call:

```
lm(formula = cheact ~ type * sex)
```

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|---------|--------|--------|-------|--------|
| | -256.48 | -67.24 | -6.00 | 72.76 | 263.52 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|---------------------|----------|------------|---------|------------|
| (Intercept) | 468.00 | 34.15 | 13.704 | <2e-16 *** |
| typetimecourse | 48.48 | 38.53 | 1.259 | 0.212 |
| sexM | 27.56 | 48.29 | 0.571 | 0.570 |
| typetimecourse:sexM | -46.04 | 54.57 | -0.844 | 0.401 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 S S 1

Residual standard error: 102.4 on 79 degrees of freedom
 Multiple R-squared: 0.02149, Adjusted R-squared: -0.01567
 F-statistic: 0.5784 on 3 and 79 DF, p-value: 0.6309

Call:

```
lm(formula = cheact ~ type + sex)
```

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|----------|---------|--------|--------|---------|
| | -251.568 | -65.778 | -5.529 | 76.432 | 268.432 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|----------------|----------|------------|---------|------------|
| (Intercept) | 486.027 | 26.590 | 18.279 | <2e-16 *** |
| typetimecourse | 25.541 | 27.238 | 0.938 | 0.351 |
| sexM | -8.498 | 22.452 | -0.379 | 0.706 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 S S 1

Residual standard error: 102.3 on 80 degrees of freedom
 Multiple R-squared: 0.01268, Adjusted R-squared: -0.01201
 F-statistic: 0.5136 on 2 and 80 DF, p-value: 0.6003

The controls are homogeneous, over time, between genders, and between study types. We set up a single control for all the pnd11 animals in 46615301.

The following code sets up a factor to handle the control values we need:

```
> dta$Controls <- with(dta, interaction(mrid, sex, age, type, tmpstds, drop = TRUE, sep = ":"))  

> lvls <- levels(dta$Controls)  

> lvls[grep("Padilla.*timecourse", lvls)] <- "padilla:timecourse"
```

```
> lvls[grep("^Padilla.*doseresponse", lvls)] <- "padilla:doseresponse"
> lvls <- sub("46615301:(F|M):adult:.*", "46615301:adult", lvls)
> lvls <- sub("46615301:(F|M):pnd11:.*", "46615301:pnd11", lvls)
> levels(dta$Controls) <- lvls
```

2.4 Levels for tz, lg, 1D, and 1Tr

The log benchmark dose, 1D, will have a random component (among mrids) in the final analysis, and in addition, will take on different values by sex and age. This may be collapsed after testing for differences between sexes, and contrasts between ages will be calculated. Since only the dose-response portions of the data provide information about 1D, we need to pair the one time-course-only mrid (44472001) with a dose-response mrid. This will be (somewhat arbitrarily) 44254401

Whether we can estimate values for lg and/or tz at all depends critically on the experimental design. In particular, unless the doses are great enough that inhibition approaches a plateau, tz will not be well identified. If there are no doses low enough to determine a low-dose plateau, lg will be governed by the shape of the dose-response curve at higher doses, as the response levels out with increasing dose. In that case, experience shows that lg and tz are strongly confounded. The plots of the adult dose-response data above suggest that lg may be positive, and that the dose-response levels off at the higher doses. There are certainly not enough data to estimate separate values of lg and tz for each dataset, but we may be able to borrow across datasets. So, we will try fitting common value for both sexes for these two parameters, pooling across all adult datasets. When we compare adult to pnd11 values in 46615301, we will just set tz = -10, as there is clearly no way to estimate that parameter from these data, as the doses in that study are too low to allow the response to even begin to plateau.

The (log) half-life parameter, 1Tr, is estimable in adults from two datasets. Rather than assign dose-response datasets to one or the other time-course dataset, we just estimate a pooled value over the whole set of data for each sex.

Finally, estimate a separate variance constant for each study X sex combination. Setup of factors to allow the above:

```
> dta$mrid2 <- dta$mrid
> lvls <- levels(dta$mrid)
> lvls[lvls == "44472001"] <- "44254401"
> levels(dta$mrid2) <- lvls
> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE, sep = ":"))
```

3 Adult Dose-Response Modeling

3.1 strategy

Use the model with simple exponential recovery (`tcmfn4()`). It looks as if the time to peak effect for all these chemicals is likely to be less than a half-hour, so the exponential recovery model is probably indistinguishable from the one with the more complex time course.

Fitting the model will follow these steps:

1. First, use `GetInitialValues()` to get starting values for the model against these data, and determine whether we can estimate lg and tz of the dose-response parameters.
2. Next, fit `tcmfn4()` using the parameterizations determined in the previous step. Since there are three data sets, use `nlme()`, with a random effect for mrid. Both time course studies were done at about the same dose, so fit a single value for 1Tr (initially, for each sex and mrid).

Set up an adult-only dataset:

```
> dta.a <- CleanUp(subset(dta, age == "adult"))
```

3.2 Initial Values

Save the initial values so that we do not need to go through all this to re-run the analysis. Also, set the argument delta to 0.5, the earliest non-zero time point.

```
> formals(tcfn4)$delta <- min(dta$tmpsts[dta$tmpsts > 0])
> initfile <- paste("initvals-RBC-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+   lA.start <- lm(I(log(cheact)) ~ Controls - 1, data = CleanUp(subset(dta.a, dose2 %in% 0)))
+   Start <- c(coef(lA.start), rep(log(0.5), nlevels(dta.a$mrid)), 0, -2, log(1), log(1.5))
+   init1 <- GetInitialValues(cheact ~ tcfn4(dose2, tmpsts, lA = lA, lD = lD, lg = lg, lTr = lTr),
+     Controls - 1, lD ~ mrid + sex - 1, tz ~ 1, lg ~ 1, lTr ~ 1), start = Start, weights = varComb(
+     mridXsex), varPower(value = 1)))
+   save(init1, file = initfile)
+ } else load(initfile)
> tmp <- t(init1$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:7], digits = 2)

 [,1] [,2] [,3] [,4] [,5] [,6] [,7]
CondIndex 17.68 5.53 3.70 2.69 2.58 2.46 2.30
mu 0.11 0.34 0.51 0.70 0.73 0.77 0.82
lD.mrid44254401 0.74 0.02 0.00 0.09 0.01 0.08 0.01
lD.mrid44472001 0.93 0.00 0.00 0.00 0.04 0.00 0.00
lD.mridPadilla 0.87 0.03 0.03 0.03 0.00 0.01 0.00
lD.mrid46615301 0.93 0.01 0.01 0.02 0.01 0.00 0.01
lD.sexM 0.04 0.03 0.84 0.01 0.00 0.01 0.02
tz 0.13 0.73 0.01 0.06 0.00 0.00 0.04
lg 0.98 0.00 0.01 0.00 0.00 0.00 0.00
lTr 0.02 0.83 0.04 0.03 0.00 0.00 0.03
```

The above shows the results of a redundancy analysis. The largest condition index is about 18, with strong loadings with all levels of lD and lg. More important, perhaps, is that after an initial optimization, the estimated values for tz are quite small, with very large standard errors:

```
> cbind(est = getParms("^tz", init1$start$beta), se = getParms("^tz", init1$Redundancy[[1]]$SE))

  est      se
tz -9.8 4577.608
```

Set tz to -10, and do not estimate it. Rerun GetInitialValues() with this reduced model:

```
> formals(tcfn4)$tz <- -10
> initfile <- paste("initvals-RBC-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+   Start <- init1$start$beta
+   Start <- Start[-grep("^tz", names(Start))]
+   init2 <- GetInitialValues(cheact ~ tcfn4(dose2, tmpsts, lA = lA, lD = lD, lg = lg, lTr = lTr),
+     Controls - 1, lD ~ mrid + sex - 1, lg ~ 1, lTr ~ 1), start = Start, weights = varComb(varIdent,
+     varPower(value = 1)))
+   save(init2, file = initfile)
+ } else load(initfile)
> tmp <- t(init2$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:7], digits = 2)
```

| | [,1] | [,2] | [,3] | [,4] | [,5] | [,6] | [,7] |
|-----------------|-------|------|------|------|------|------|------|
| CondIndex | 23.08 | 4.29 | 3.14 | 2.63 | 2.54 | 2.49 | 2.09 |
| mu | 0.08 | 0.42 | 0.57 | 0.68 | 0.71 | 0.72 | 0.86 |
| 1D.mrid44254401 | 0.84 | 0.00 | 0.09 | 0.01 | 0.00 | 0.03 | 0.00 |
| 1D.mrid44472001 | 0.94 | 0.00 | 0.00 | 0.04 | 0.01 | 0.00 | 0.00 |
| 1D.mridPadilla | 0.97 | 0.02 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 |
| 1D.mrid46615301 | 0.93 | 0.01 | 0.01 | 0.01 | 0.02 | 0.00 | 0.00 |
| 1D.sexM | 0.05 | 0.90 | 0.00 | 0.00 | 0.00 | 0.00 | 0.02 |
| lg | 0.99 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| lTr | 0.07 | 0.00 | 0.70 | 0.00 | 0.01 | 0.09 | 0.03 |

Fit the model first with `gnls()` to get the variance model right.

```
> Start <- Start0 <- init2$start$beta
> icnt <- 1
> Maxcnt <- 50
> repeat {
+   drmod1 <- try(gnls(cheact ~ tcmlfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data =
+     Controls - 1, lD ~ mrid + sex - 1, lg ~ 1, lTr ~ 1), start = Start), silent = TRUE)
+   if (!inherits(drmod1, "try-error") || icnt > Maxcnt) {
+     if (icnt <= Maxcnt)
+       writeLines(paste("Successful in ", icnt, if (icnt > 1)
+         "tries"
+         else "try"))
+     else writeLines("Maxcnt exceeded")
+     break
+   }
+   icnt <- icnt + 1
+   Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }
```

Successful in 1 try

That works.

Now, two more models. The next one allows standard deviation to vary among studies, and the one after includes a power function in the model for the standard deviation:

```
> Start0 <- coef(drmod1)
> Start <- Start0
> icnt <- 1
> Maxcnt <- 50
> repeat {
+   drmod2 <- try(gnls(cheact ~ tcmlfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data =
+     Controls - 1, lD ~ mrid + sex - 1, lg ~ 1, lTr ~ 1), weights = varIdent(form = ~1 | mrid*sex)
+     silent = TRUE)
+   if (!inherits(drmod2, "try-error") || icnt > Maxcnt) {
+     if (icnt <= Maxcnt)
+       writeLines(paste("Successful in ", icnt, if (icnt > 1)
+         "tries"
+         else "try"))
+     else writeLines("Maxcnt exceeded")
+     break
+   }
+   icnt <- icnt + 1
+   Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }
```

```

Successful in 5 tries

> Start0 <- coef(drmmod2)
> Start <- Start0
> icnt <- 1
> Maxcnt <- 50
> repeat {
+   drmod3 <- try(gnls(cheact ~ tcmlfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data =
+     Controls - 1, lD ~ mrid + sex - 1, lg ~ 1, lTr ~ 1), weights = varComb(varIdent(form =
+       start = Start), silent = TRUE)
+   if (!inherits(drmmod3, "try-error") || icnt > Maxcnt) {
+     if (icnt <= Maxcnt)
+       writeLines(paste("Successful in ", icnt, if (icnt > 1)
+         "tries"
+         else "try"))
+     else writeLines("Maxcnt exceeded")
+     break
+   }
+   icnt <- icnt + 1
+   Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }

```

Successful in 1 try

```
> anova(drmmod1, drmod2, drmod3)
```

| Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|--------|------|----------|----------|-----------|--------|----------|---------|
| drmod1 | 1 27 | 8042.957 | 8165.643 | -3994.479 | | | |
| drmod2 | 2 33 | 8033.247 | 8183.196 | -3983.624 | 1 vs 2 | 21.71001 | 0.0014 |
| drmod3 | 3 34 | 7999.218 | 8153.711 | -3965.609 | 2 vs 3 | 36.02967 | <.0001 |

Yes. We will use the model in drmod3.

Fit the same model as above as a mixed effect model, except just allow lD to vary among sexes, and include a random effect for the variation of lD among studies.

```

> Par <- coef(drmmod3)
> lDpar <- getParms("^lD", Par)
> lD.sexF <- mean(lDpar[grep("mrid", names(lDpar))])
> Start0 <- c(getParms("^lA", Par), lD.sexF, getParms("lD\\sexM", Par), getParms("^lg", Par), getParms(
> RE <- matrix(lDpar[grep("mrid", names(lDpar))] - mean(lDpar[grep("mrid", names(lDpar))])), ncol = 1, c
+   NULL)
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 30
> repeat {
+   drmod4 <- try(nlme(cheact ~ tcmlfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data =
+     Controls - 1, lD ~ sex, lg ~ 1, lTr ~ 1), random = lD ~ 1 | mrid, weights = varComb(varIdent(
+       varPower(value = 0.5)), start = Start), silent = TRUE)
+   if (!inherits(drmmod4, "try-error") || icnt > Maxcnt) {
+     if (icnt <= Maxcnt)
+       writeLines(paste("Success after", icnt, "try(s)."))
+     else writeLines(paste("Maxcnt,", Maxcnt, "exceeded"))
+     break
+   }
+   Start <- list(fixed = Start0 * (1 + rnorm(length(Start0), sd = 0.2)), random = RE)
+   icnt <- icnt + 1
+ }
```

Success after 1 trie(s).

The interesting fitted values:

```
> nms <- names(fixed.effects(drmod4))
> summary(drmod4)$tTable[-grep("^lA", nms), ]

      Value Std.Error DF t-value p-value
1D.(Intercept) -1.89467644 0.33200223 669 -5.706818 1.729984e-08
1D.sexM         0.06410982 0.06549665 669  0.978826 3.280198e-01
lg              0.51417821 0.16601707 669  3.097141 2.035711e-03
lTr             -0.27088119 0.08011063 669 -3.381339 7.633088e-04
```

Note, particularly, that the difference between the sexes in 1D is not significant. Refit the data with the simpler term for 1D:

```
> Par <- fixed.effects(drmod4)
> Start0 <- c(getParms("^lA", Par), Par["1D.(Intercept)"], getParms("^lg", Par), getParms("^lTr", Par))
> RE <- data.matrix(random.effects(drmod4))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 30
> repeat {
+   drmod5 <- try(nlme(cheact ~ tcmlfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data =
+     Controls = 1, lD ~ 1, lg ~ 1, lTr ~ 1), random = lD ~ 1 | mrid, weights = varComb(varIdent(fo
+     varPower(value = 0.5)), start = Start), silent = TRUE)
+   if (!inherits(drmod5, "try-error") || icnt > Maxcnt) {
+     if (icnt <= Maxcnt)
+       writeLines(paste("Success after", icnt, "trie(s)."))
+     else writeLines(paste("Maxcnt,", Maxcnt, "exceeded"))
+     break
+   }
+   Start <- list(fixed = Start0 * (1 + rnorm(length(Start0), sd = 0.2)), random = RE)
+   icnt <- icnt + 1
+ }
```

Success after 1 trie(s).

```
> Ints.a <- intervals(drmod5, which = "fixed")$fixed
> Ints90.a <- intervals(drmod5, which = "fixed", level = 0.9)$fixed
> tTab.a <- summary(drmod5)$tTable
> summary(drmod5)
```

Nonlinear mixed-effects model fit by maximum likelihood
 Model: cheact ~ tcmlfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
 Data: dta.a
 AIC BIC logLik
 8015.282 8156.144 -3976.641

Random effects:
 Formula: lD ~ 1 | mrid
 1D Residual
 StdDev: 0.4436803 2.837178

Combination of variance functions:
 Structure: Different standard deviations per stratum

Formula: ~1 | mridXsex

Parameter estimates:

| | | | | | | |
|------------|------------|------------|------------|-----------|------------|------------|
| 44254401:M | 44254401:F | 44472001:M | 44472001:F | Padilla:M | 46615301:M | 46615301:F |
| 1.0000000 | 0.9797364 | 0.8779524 | 0.7994279 | 0.9513795 | 1.1192736 | 1.0983174 |

Structure: Power of variance covariate

Formula: ~fitted(.)

Parameter estimates:

| | |
|-------|-----------|
| power | 0.5644341 |
|-------|-----------|

Fixed effects: list(lA ~ Controls ~ 1, lD ~ 1, lg ~ 1, lTr ~ 1)

| | Value | Std.Error | DF | t-value | p-value |
|--|-----------|-----------|-----|-----------|---------|
| lA.Controls44254401:F:adult:doseresponse:-1 | 6.045242 | 0.0320929 | 670 | 188.36678 | 0.0000 |
| lA.Controls44254401:M:adult:doseresponse:-1 | 5.846728 | 0.0357151 | 670 | 163.70463 | 0.0000 |
| lA.Controls46615301:adult | 6.060110 | 0.0235003 | 670 | 257.87345 | 0.0000 |
| lA.Controls44472001:F:adult:timecourse:0.5 | 6.059645 | 0.0483701 | 670 | 125.27673 | 0.0000 |
| lA.Controls44472001:M:adult:timecourse:0.5 | 5.868303 | 0.0559078 | 670 | 104.96394 | 0.0000 |
| lA.Controlspadilla:timecourse | 6.148049 | 0.0452095 | 670 | 135.99021 | 0.0000 |
| lA.Controlspadilla:doseresponse | 5.669074 | 0.0569464 | 670 | 99.55105 | 0.0000 |
| lA.Controls44254401:F:adult:doseresponse:1 | 6.023645 | 0.0449177 | 670 | 134.10400 | 0.0000 |
| lA.Controls44254401:M:adult:doseresponse:1 | 6.063494 | 0.0434153 | 670 | 139.66258 | 0.0000 |
| lA.Controls44472001:F:adult:timecourse:2 | 6.034582 | 0.0396437 | 670 | 152.22038 | 0.0000 |
| lA.Controls44472001:M:adult:timecourse:2 | 5.944609 | 0.0449725 | 670 | 132.18312 | 0.0000 |
| lA.Controls44472001:F:adult:timecourse:3 | 5.938532 | 0.0397265 | 670 | 149.48552 | 0.0000 |
| lA.Controls44472001:M:adult:timecourse:3 | 6.036938 | 0.0417560 | 670 | 144.57639 | 0.0000 |
| lA.Controls44472001:F:adult:timecourse:4 | 5.968959 | 0.0386111 | 670 | 154.59185 | 0.0000 |
| lA.Controls44472001:M:adult:timecourse:4 | 6.140531 | 0.0393456 | 670 | 156.06658 | 0.0000 |
| lA.Controls44254401:F:adult:doseresponse:24 | 5.912962 | 0.0339963 | 670 | 173.92945 | 0.0000 |
| lA.Controls44254401:M:adult:doseresponse:24 | 5.876140 | 0.0357097 | 670 | 164.55318 | 0.0000 |
| lA.Controls44254401:F:adult:doseresponse:360 | 5.838605 | 0.0351154 | 670 | 166.26901 | 0.0000 |
| lA.Controls44254401:M:adult:doseresponse:360 | 5.893024 | 0.0350021 | 670 | 168.36198 | 0.0000 |
| lD | -1.871289 | 0.3288189 | 670 | -5.69094 | 0.0000 |
| lg | 0.508678 | 0.1664895 | 670 | 3.05532 | 0.0023 |
| lTr | -0.276912 | 0.0798519 | 670 | -3.46782 | 0.0006 |

Correlation:

| | lA.C44254401:F:::- | lA.C44254401:M:::- | lA.C46 | lA.C44472001: |
|--|--------------------|--------------------|--------|---------------|
| lA.Controls44254401:M:adult:doseresponse:-1 | 0.000 | | | |
| lA.Controls46615301:adult | 0.000 | 0.000 | | |
| lA.Controls44472001:F:adult:timecourse:0.5 | 0.000 | 0.000 | -0.003 | |
| lA.Controls44472001:M:adult:timecourse:0.5 | 0.000 | 0.000 | -0.002 | 0.181 |
| lA.Controlspadilla:timecourse | 0.000 | 0.000 | 0.030 | -0.007 |
| lA.Controlspadilla:doseresponse | 0.000 | 0.000 | 0.066 | -0.004 |
| lA.Controls44254401:F:adult:doseresponse:1 | 0.000 | 0.000 | 0.062 | -0.005 |
| lA.Controls44254401:M:adult:doseresponse:1 | 0.000 | 0.000 | 0.067 | -0.009 |
| lA.Controls44472001:F:adult:timecourse:2 | 0.000 | 0.000 | 0.030 | 0.040 |
| lA.Controls44472001:M:adult:timecourse:2 | 0.000 | 0.000 | 0.026 | 0.035 |
| lA.Controls44472001:F:adult:timecourse:3 | 0.000 | 0.000 | 0.019 | 0.013 |
| lA.Controls44472001:M:adult:timecourse:3 | 0.000 | 0.000 | 0.018 | 0.013 |
| lA.Controls44472001:F:adult:timecourse:4 | 0.000 | 0.000 | 0.011 | 0.005 |
| lA.Controls44472001:M:adult:timecourse:4 | 0.000 | 0.000 | 0.011 | 0.005 |
| lA.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | 0.000 |
| lA.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | 0.000 |
| lA.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | 0.000 |
| lA.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | 0.000 |
| lD | 0.000 | 0.000 | -0.142 | -0.014 |

| | | | | |
|--|--------------------|--------------------|--------------------|--------|
| lg | 0.000 | 0.000 | -0.174 | 0.006 |
| lTr | 0.000 | 0.000 | 0.136 | -0.029 |
| | 1A.Cntrlspdll:d | 1A.C44254401:F:::1 | 1A.C44254401:M:::1 | 1A.C |
| 1A.Controls44254401:M:adult:doseresponse:-1 | | | | |
| 1A.Controls46615301:adult | | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | | |
| 1A.Controlspadilla:timecourse | | | | |
| 1A.Controlspadilla:doseresponse | | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | 0.099 | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | 0.098 | 0.224 | | |
| 1A.Controls44472001:F:adult:timecourse:2 | 0.037 | 0.054 | 0.076 | |
| 1A.Controls44472001:M:adult:timecourse:2 | 0.033 | 0.047 | 0.067 | 0.0 |
| 1A.Controls44472001:F:adult:timecourse:3 | 0.024 | 0.034 | 0.049 | 0.0 |
| 1A.Controls44472001:M:adult:timecourse:3 | 0.022 | 0.033 | 0.046 | 0.0 |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.013 | 0.019 | 0.028 | 0.0 |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.013 | 0.019 | 0.027 | 0.0 |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | 0.0 |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | 0.0 |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | 0.0 |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | 0.0 |
| 1D | -0.250 | -0.215 | -0.173 | -0.0 |
| lg | -0.337 | -0.251 | -0.224 | -0.0 |
| lTr | 0.168 | 0.245 | 0.349 | 0.2 |
| | 1A.C44472001:F:::3 | 1A.C44472001:M:::3 | 1A.C44472001:F:::4 | 1 |
| 1A.Controls44254401:M:adult:doseresponse:-1 | | | | |
| 1A.Controls46615301:adult | | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | | |
| 1A.Controlspadilla:timecourse | | | | |
| 1A.Controlspadilla:doseresponse | | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | | | | |
| 1A.Controls44472001:F:adult:timecourse:3 | | | | |
| 1A.Controls44472001:M:adult:timecourse:3 | 0.020 | | | |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.012 | 0.011 | | |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.011 | 0.011 | 0.006 | |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | |
| 1D | -0.024 | -0.023 | -0.013 | - |
| lg | -0.041 | -0.039 | -0.023 | - |
| lTr | 0.139 | 0.132 | 0.079 | |
| | 1A.C44254401:M:::2 | 1A.C44254401:F:::3 | 1A.C44254401:M:::3 | 1 |
| 1A.Controls44254401:M:adult:doseresponse:-1 | | | | |
| 1A.Controls46615301:adult | | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | | |
| 1A.Controlspadilla:timecourse | | | | |
| 1A.Controlspadilla:doseresponse | | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | | |

1A.Controls44254401:M:adult:doseresponse:1
1A.Controls44472001:F:adult:timecourse:2
1A.Controls44472001:M:adult:timecourse:2
1A.Controls44472001:F:adult:timecourse:3
1A.Controls44472001:M:adult:timecourse:3
1A.Controls44472001:F:adult:timecourse:4
1A.Controls44472001:M:adult:timecourse:4
1A.Controls44254401:F:adult:doseresponse:24
1A.Controls44254401:M:adult:doseresponse:24
1A.Controls44254401:F:adult:doseresponse:360 0.000
1A.Controls44254401:M:adult:doseresponse:360 0.000 0.000
1D 0.000 0.000 0.000
lg 0.000 0.000 0.000
1Tr 0.000 0.000 0.000

Standardized Within-Group Residuals:

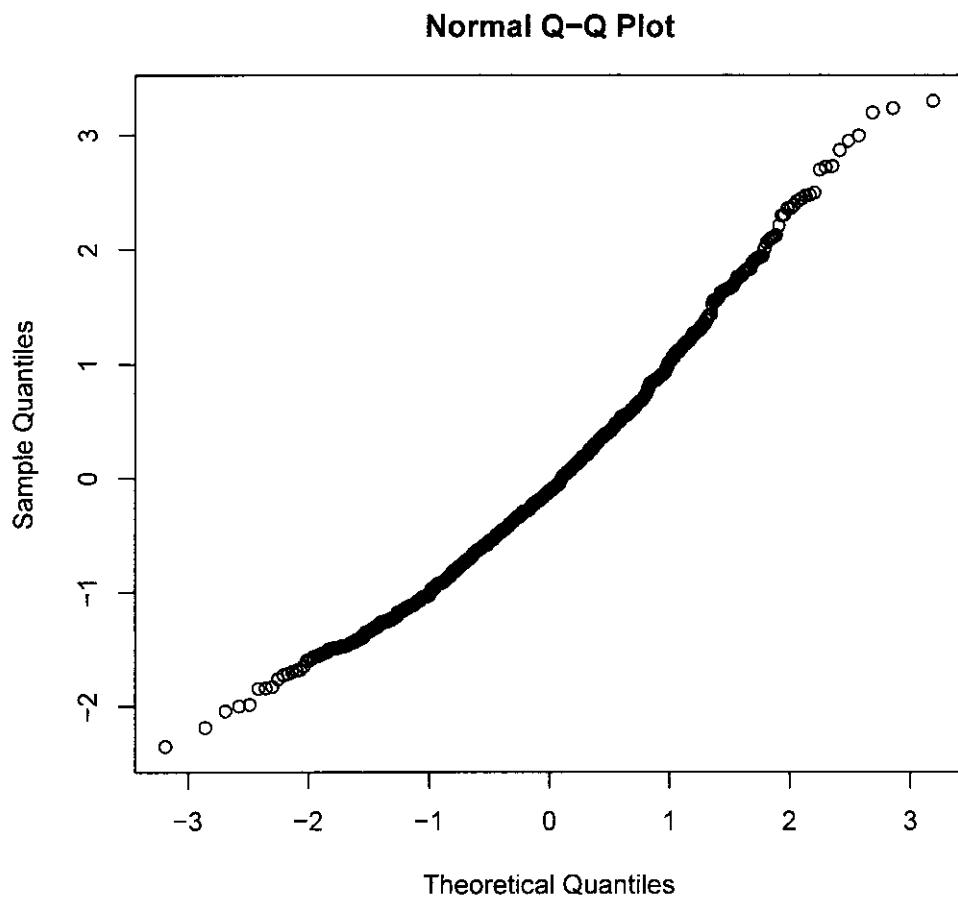
| Min | Q1 | Med | Q3 | Max |
|------------|------------|------------|-----------|-----------|
| -2.3502493 | -0.7200896 | -0.1209655 | 0.5758003 | 3.2966788 |

Number of Observations: 695

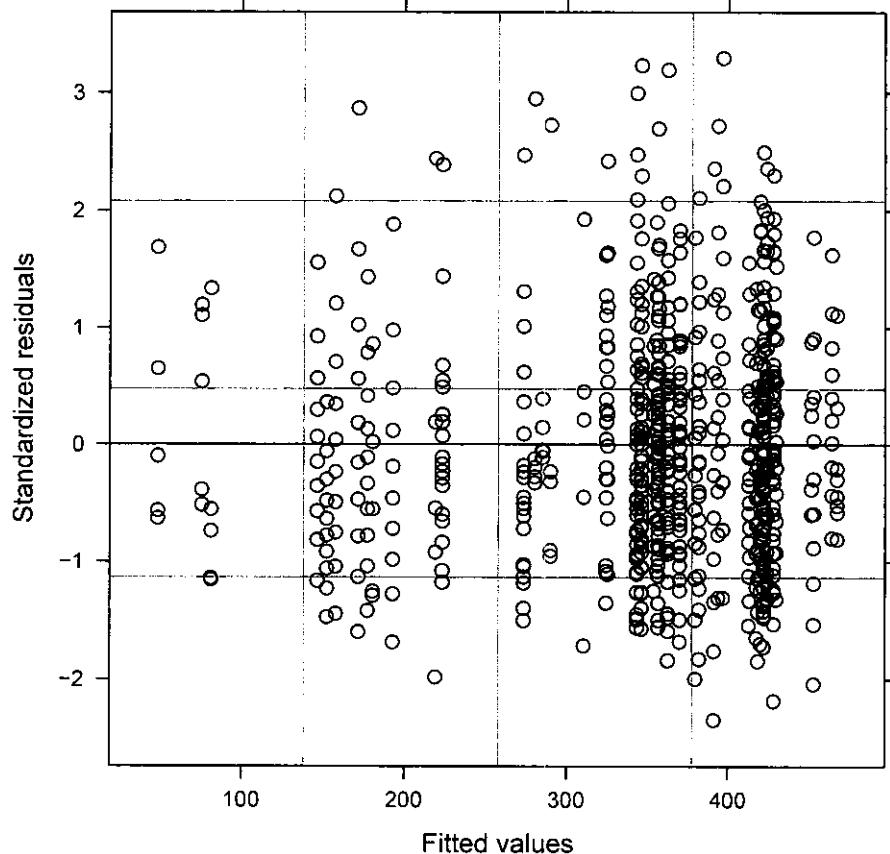
Number of Groups: 4

Diagnostic plots for this model:

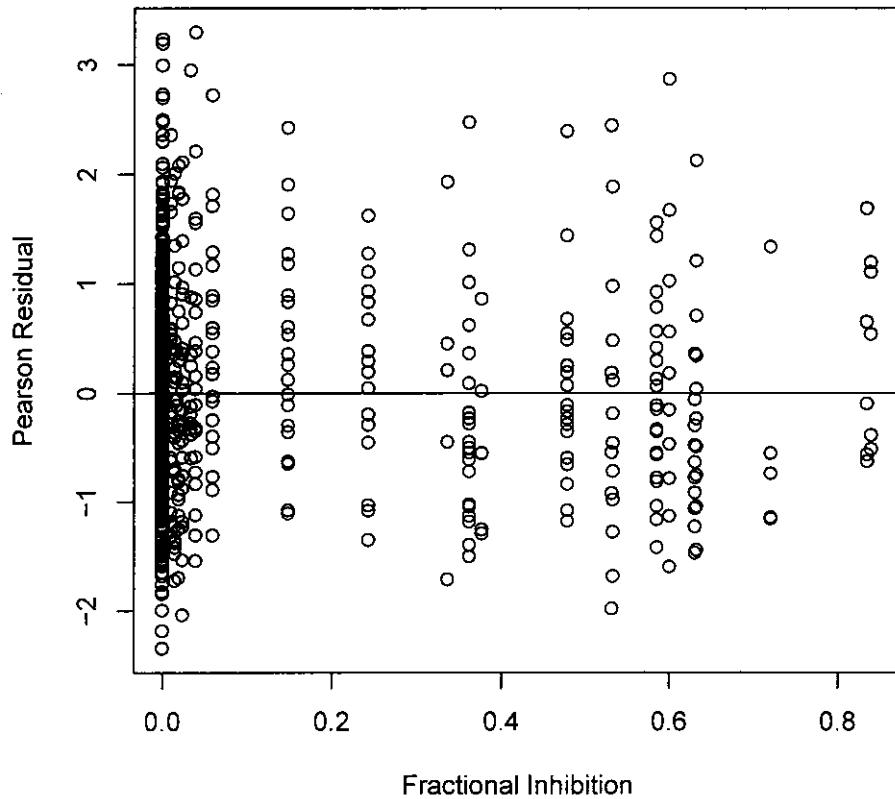
QQ Plot of (Pearson) Scaled Residuals



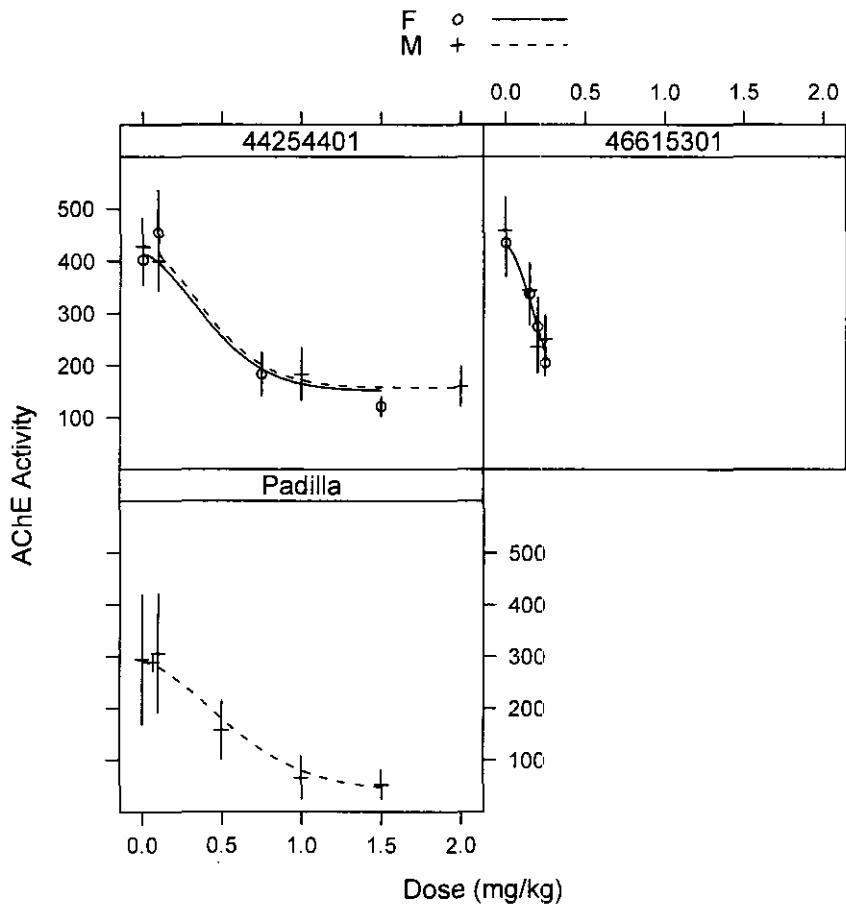
Scaled Residuals versus Fitted Activity Level



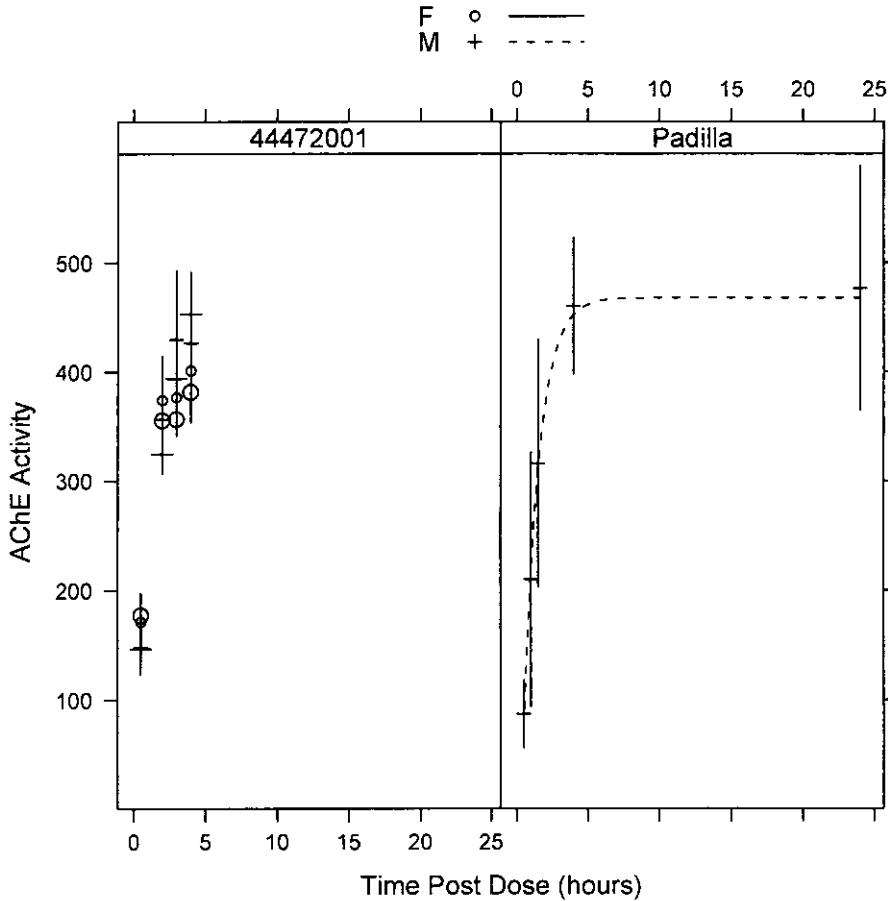
Scaled Residuals versus Fitted Fraction of Inhibition



Next, dose-response and recovery curves with means and 95% confidence intervals from the data.



Timecourses:



In the time course plot for 44472001, the larger symbols correspond to the fitted value for that sex and time point from the model.

4 Analysis of PND11 to Adult Potency Ratios in MRID 46615301

This MRID contain both PND11 and adult dose response information and pnd11 time-course information that can be used to evaluate the ratio of potencies between adults and juveniles.

Extract the data for this subanalysis, and summarize the design used:

```
> dta.ajr <- CleanUp(subset(dta, mrid == "46615301"))
> with(dta.ajr, print(table(dose, tmpstds, age), zero.print = "."))
, , age = adult

      tmpstds
dose   0.5 1 1.5 2 3 4 6
  0     20 . . . . 17 .
  0.075 . . . . . .
  0.1   . . . . . .
  0.125 . . . . . .
  0.15   20 . . . . 20 .
  0.2     20 . . . . 20 .
```

```

0.25 20 . . . 20 .

, , age = pnd11

tmpstds
dose 0.5 1 1.5 2 3 4 6
0 18 10 . 10 . 8 .
0.075 19 . . . .
0.1 26 10 9 9 10 10 9
0.125 19 . . . . .
0.15 20 . . . . .
0.2 . . . . .
0.25 . . . . .

```

Two features stand out here: there is no time course component in the adult dataset (the analysis of the adult data, above, shows that AChE activity has pretty much returned to normal by four hours, so that time point is useless for estimating recovery half life), and there are no controls for three of the seven pnd11 time points. Furthermore, the analysis of the pnd11 control groups reported above shows that they are homogeneous.

The dose-response component of both age groups was carried out at 0.5 hours after dosing. That value will be the "delta" in the dose-time response model. If we drop the four hour data in the adults, we only need a half-life parameter in the pnd11 animals, as the dose-response data, at 0.5 hour, will be time "0" in the model. Dropping this time group allows us to simultaneously estimate the dose-response and timecourse parameters, simplifying the analysis. There is minimal disadvantage, since AChE activity has substantially recovered by four hours.

```
> dta.ajr <- CleanUp(subset(dta.ajr, (age == "pnd11") | (age == "adult" & tmpstds == 0.5)))
```

Since there is only a single mrid, there are no random effects to consider. We will use generalized non-linear least squares to fit the model, allowing for a power variance model. In addition, given the relatively low levels of inhibition seen in this study, we will not try to estimate the horizontal asymptote parameterized by tz.

Get initial values:

```

> formals(tcmfn4)$delta <- min(dta.ajr$tmpstds[dta.ajr$tmpstds > 0])
> formals(tcmfn4)$tz <- -10
> initfile <- paste("initvals-RBC-DR-6.RData", sep = "")
> if (!file.exists(initfile)) {
+   lA.start <- lm(I(log(cheact)) ~ Controls - 1, data = CleanUp(subset(dta.ajr, dose %in% 0)))
+   lA.start <- coef(lA.start)[paste("Controls", levels(dta.ajr$Controls), sep = "")]
+   names(lA.start) <- levels(dta.ajr$Controls)
+   mn <- mean(lA.start, na.rm = TRUE)
+   lA.start[is.na(lA.start)] <- mn
+   Start <- with(dta.ajr, c(lA.start, rep(-0.72, nlevels(sex:age)), rep(0, nlevels(sex:age)), rep(1,
+     init6 <- GetInitialValues(cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), d
+       Controls - 1, lD ~ age:sex - 1, lg ~ age:sex - 1, lTr ~ sex - 1), start = Start, weights = va
+       save(init6, file = initfile)
+   } else load(initfile)
> tmp <- t(init6$Redundancy[[1]]$Eigens)
> round(tmp[, 1:6], digits = 2)

 [,1] [,2] [,3] [,4] [,5] [,6]
CondIndex          14.75 11.40 9.20 8.06 3.10 2.53
mu                0.11  0.15  0.18  0.21  0.53  0.65
lA.Controls46615301:adult 0.11  0.09  0.00  0.00  0.00  0.76
lA.Controls46615301:pnd11 0.00  0.00  0.18  0.03  0.74  0.00
lD.ageadult:sexF    0.07  0.92  0.00  0.00  0.00  0.00
lD.agepnd11:sexF   0.00  0.00  0.25  0.73  0.00  0.00

```

| | | | | | | |
|------------------|------|------|------|------|------|------|
| 1D.ageadult:sexM | 0.97 | 0.02 | 0.00 | 0.00 | 0.00 | 0.00 |
| 1D.agepnd11:sexM | 0.00 | 0.00 | 0.85 | 0.13 | 0.00 | 0.00 |
| lg.ageadult:sexF | 0.05 | 0.93 | 0.00 | 0.00 | 0.00 | 0.01 |
| lg.agepnd11:sexF | 0.00 | 0.00 | 0.20 | 0.76 | 0.02 | 0.00 |
| lg.ageadult:sexM | 0.96 | 0.03 | 0.00 | 0.00 | 0.00 | 0.01 |
| lg.agepnd11:sexM | 0.00 | 0.00 | 0.79 | 0.18 | 0.02 | 0.00 |
| lTr.sexF | 0.00 | 0.00 | 0.00 | 0.04 | 0.29 | 0.00 |
| lTr.sexM | 0.00 | 0.00 | 0.00 | 0.03 | 0.27 | 0.00 |

Estimates of lg and ID are possibly confounded, but the maximum condition index is probably small enough to go ahead and try a fit. Now, the fit for the control option coded in 'Control2':

```
> Start <- init6$start$beta
> dta.ajr$A.S <- with(dta.ajr, interaction(age, sex, drop = TRUE, sep = ":")) 
> drmod6 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = 1A, lD = 1D, lg = lg, lTr = lTr), data = dta.a
+   Controls = 1, lD ~ age:sex - 1, lg ~ age:sex - 1, lTr ~ sex - 1), start = Start, weights = varCom
+   A.S), varPower(value = 1)))
```

Look for simplifications: try to collapse ID, lg, and lTr across sex:

```
> anova(drmod6, L = matrix(c(1, -1, 0, 0, 0, 0, -1, 1), nrow = 2, ncol = 4, byrow = TRUE, dimnames = li
+   "1D.ageadult:sexM", "1D.agepnd11:sexF", "1D.agepnd11:sexM")))
```

Denom. DF: 255

F-test for linear combination(s)

| | 1D.ageadult:sexF | 1D.agepnd11:sexF | 1D.ageadult:sexM | 1D.agepnd11:sexM |
|---|------------------|------------------|------------------|------------------|
| 1 | 1 | 0 | -1 | 0 |
| 2 | 0 | -1 | 0 | 1 |

| numDF | F-value | p-value |
|-------|---------|-----------|
| 1 | 2 | 0.2971038 |
| | | 0.7432 |

```
> anova(drmod6, L = matrix(c(1, -1, 0, 0, 0, 0, -1, 1), nrow = 2, ncol = 4, byrow = TRUE, dimnames = li
+   "lg.ageadult:sexM", "lg.agepnd11:sexF", "lg.agepnd11:sexM")))
```

Denom. DF: 255

F-test for linear combination(s)

| | lg.ageadult:sexF | lg.agepnd11:sexF | lg.ageadult:sexM | lg.agepnd11:sexM |
|---|------------------|------------------|------------------|------------------|
| 1 | 1 | 0 | -1 | 0 |
| 2 | 0 | -1 | 0 | 1 |

| numDF | F-value | p-value |
|-------|---------|-----------|
| 1 | 2 | 0.4224598 |
| | | 0.6559 |

```
> anova(drmod6, L = c(lTr.sexF = 1, lTr.sexM = -1))
```

Denom. DF: 255

F-test for linear combination(s)

| | lTr.sexF | lTr.sexM |
|---|----------|----------|
| 1 | 1 | -1 |

| numDF | F-value | p-value |
|-------|---------|------------|
| 1 | 1 | 0.05992136 |
| | | 0.8068 |

None of the effects differs between sexes. What is the joint significance of collapsing the remaining effects across sex, simultaneously?

```
> anova(drmod6, L = matrix(c(1, -1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
+   0, 0, 0, 0, 0, 0, -1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, -1, 1), nrow = 5, ncol = 10, byrow = TR
+   c("1D.ageadult:sexF", "1D.ageadult:sexM", "1D.agepnd11:sexF", "1D.agepnd11:sexM", "lg.ageadult:se
+   "lg.agepnd11:sexF", "lg.agepnd11:sexM", "lTr.sexF", "lTr.sexM")))
```

```

Denom. DF: 255
F-test for linear combination(s)
  1D.ageadult:sexF 1D.agepnd11:sexF 1D.ageadult:sexM 1D.agepnd11:sexM lg.ageadult:sexF lg.agepnd11:sexF
1           1           0          -1           0           0           0
2           0           1           0          -1           0           0
3           0           0           0           0           0          -1
4           0           0           0           0           0           0
5           0           0           0           0           0           0
lTr.sexM
1           0
2           0
3           0
4           0
5           1
  numDF   F-value p-value
1      5 0.2553594 0.9369

```

Now fit the simplified model:

```

> Parms <- coef(drmmod6)
> Start <- c(getParms("lA", Parms), mean(getParms("1D.ageadult", Parms)), mean(getParms("1D.agepnd11",
+   Parms)), mean(getParms("lg.agepnd11", Parms)), mean(getParms("lTr", Parms)))
> initfile <- paste("initvals-RBC-DR-7.RData", sep = "")
> if (!file.exists(initfile)) {
+   init7 <- GetInitialValues(cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), d
+     Controls - 1, lD ~ age - 1, lg ~ age - 1, lTr ~ 1), start = Start, weights = varPower(value =
+     save(init7, file = initfile)
+ } else load(initfile)
> Start <- Start0 <- init7$start$beta
> icnt <- 1
> Maxcnt <- 50
> repeat {
+   drmod7 <- try(gnls(cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data = d
+     factor(Controls) - 1, lD ~ age - 1, lg ~ age - 1, lTr ~ 1), start = Start, weights = varComb(
+     A.S), varPower(value = 1)), silent = TRUE)
+   if (!inherits(drmod7, "try-error") || icnt > Maxcnt) {
+     if (icnt <= Maxcnt)
+       writeLines(paste("Successful in ", icnt, if (icnt > 1)
+         "tries"
+         else "try"))
+     else writeLines("Maxcnt exceeded")
+     break
+   }
+   icnt <- icnt + 1
+   Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }

```

Successful in 4 tries

Finally, compare the reduced to the fuller parameterization; look at AIC and BIC, as well as the P-value for the overall comparison. Now, try the alternative control parameterization:

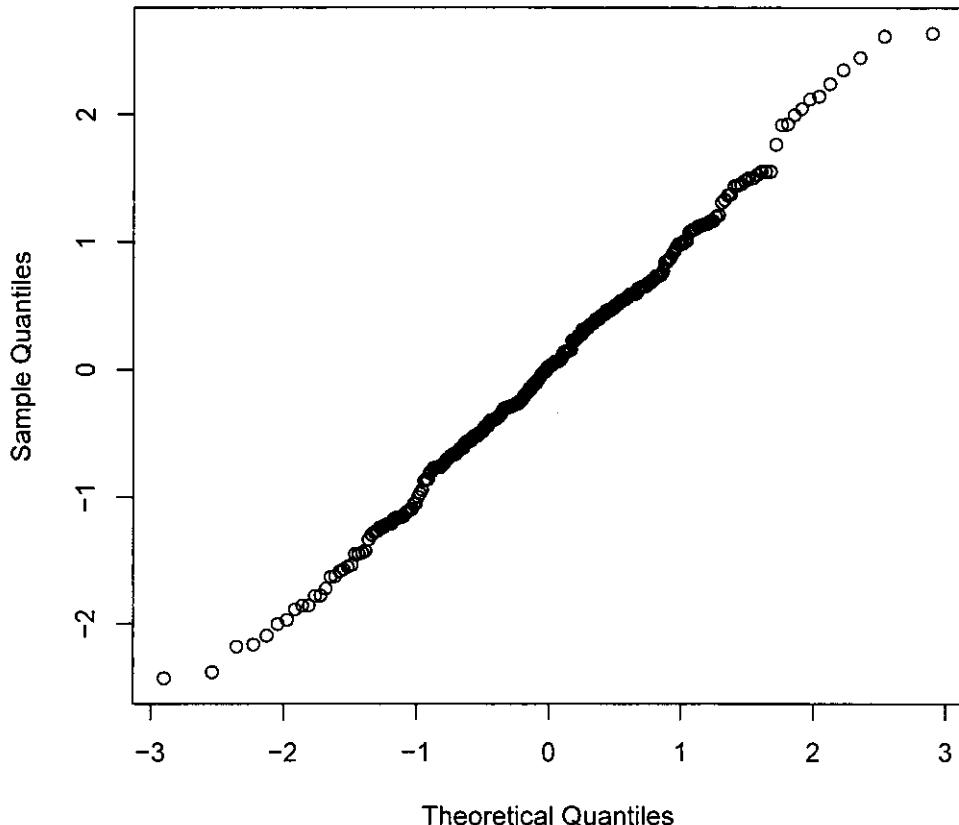
```
> anova(drmmod6, drmod7)
```

| Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|--------|------|----------|----------|-----------|--------|----------|---------|
| drmod6 | 1 17 | 3150.897 | 3211.880 | -1558.448 | | | |
| drmod7 | 2 12 | 3142.421 | 3185.468 | -1559.211 | 1 vs 2 | 1.524395 | 0.9102 |

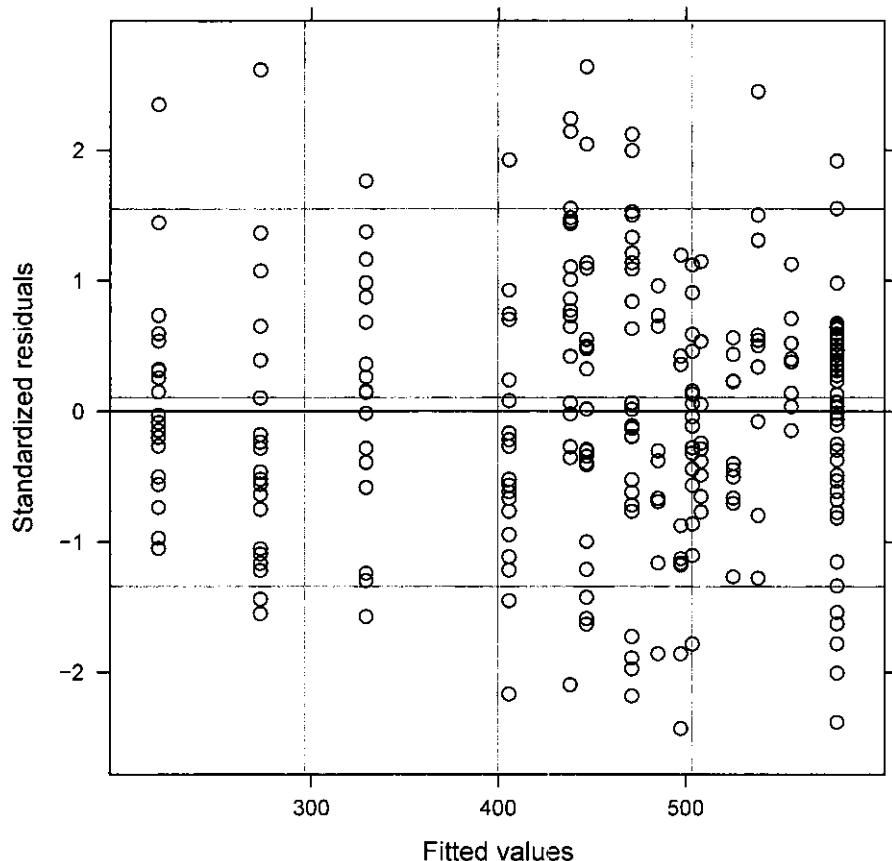
Note that the P-value is similar to that for the total contrast. The AIC and BIC for the simpler model is smaller. Diagnostic plots for this fit:

QQ Plot of (Pearson) Scaled Residuals:

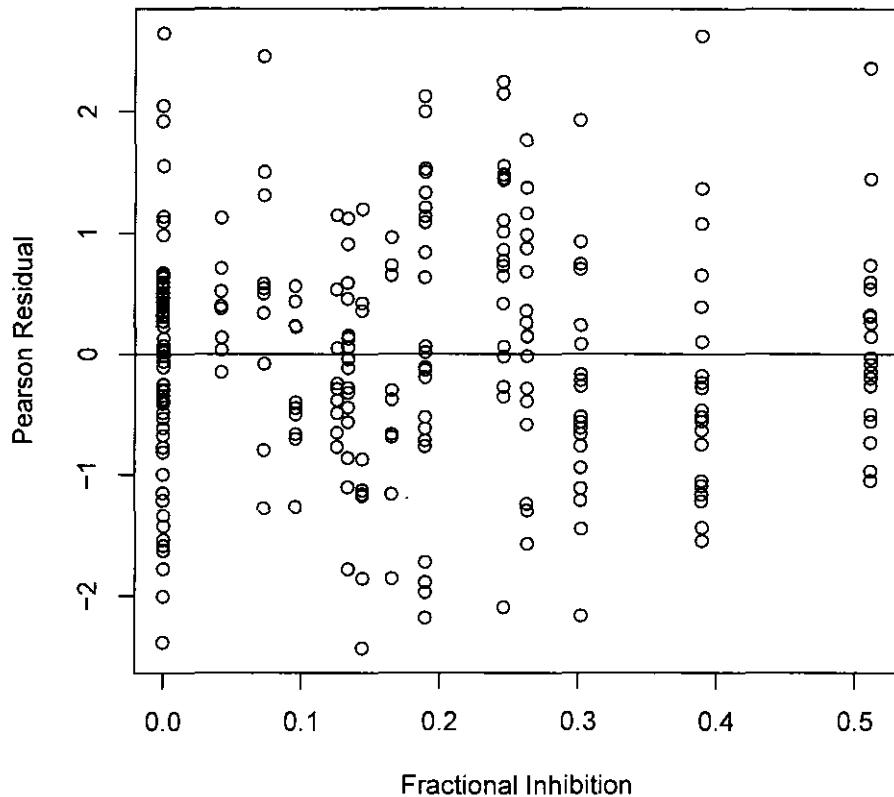
Normal Q-Q Plot



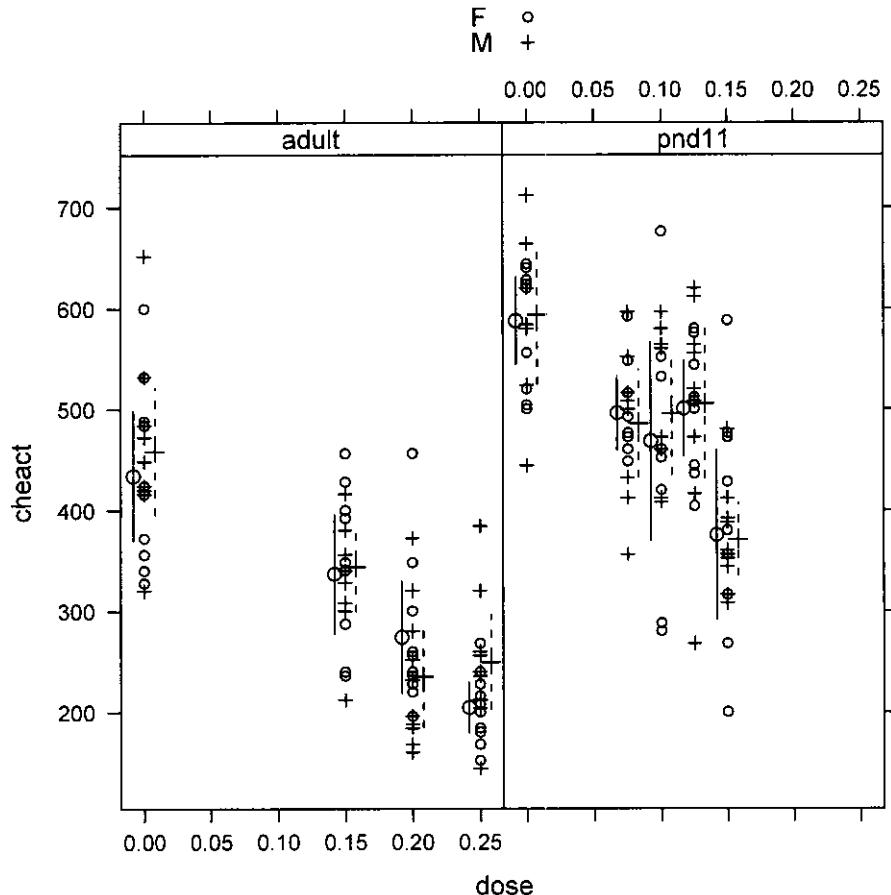
Scaled residuals versus fitted values:



Scaled Residuals versus Predicted Fraction of Inhibition:

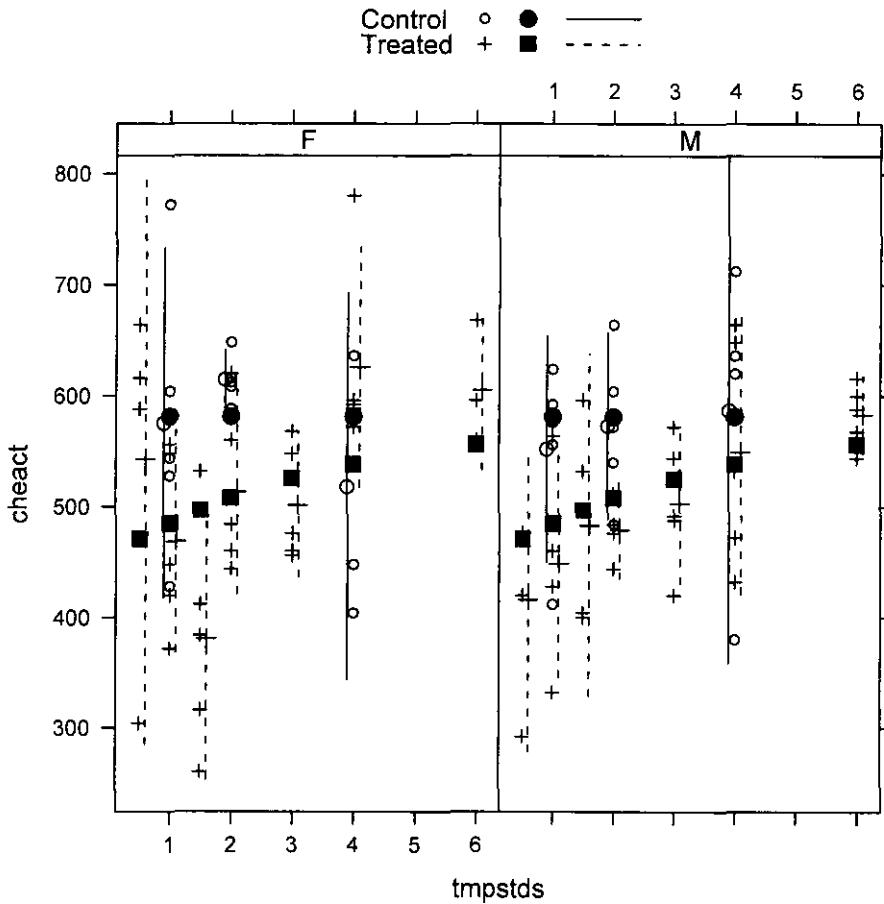


Dose-Response Curves, by age:



Here, the dose-group means for males and females are displaced slightly to the right and left, respectively, of their correct place to make it easier to distinguish the means from the raw data points.

Time Course for pnd11 Animals



Larger, solid symbols represent fitted values from the model. Confidence intervals are 95% confidence intervals for the means.

Two values of interest from this model are the ratio of the adult to the pnd11 BMDs, and the pnd11 recovery half-life. The ratio is conveniently calculated by exponentiating the difference between the log BMDs (ID) for each age group. Confidence intervals are calculated by calculating the standard error for the linear contrast of the two log BMDs, and exponentiating the approximate normal-theory confidence interval for the difference of the log BMDs. This is all carried out by the code below:

```

> cov <- drmod7$varBeta
> Cn <- coef(drmod7)
> Cn[] <- 0
> Cn["1D.ageadult"] <- 1
> Cn["1D.agepnd11"] <- -1
> lpotrat <- Cn %*% coef(drmod7)
> selpotrat <- sqrt(Cn %*% cov %*% Cn)
> potrat <- exp(lpotrat)
> CIpotrat <- exp(lpotrat + qnorm(c(0.025, 0.975)) * selpotrat)

> tTab.j <- summary(drmod7)$tTable
> Ints.j <- intervals(drmod7, which = "coef")$coef
> Ints90.j <- intervals(drmod7, which = "coef", level = 0.9)$coef
> summary(drmod7)

```

```

Generalized nonlinear least squares fit
Model: cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
Data: dta.ajr
      AIC    BIC   logLik
 3142.421 3185.468 -1559.211

```

Combination of variance functions:

Structure: Different standard deviations per stratum

Formula: ~1 | A.S

Parameter estimates:

```

pnd11:M  pnd11:F  adult:M  adult:F
1.0000000 1.1807617 0.9554461 0.9208067

```

Structure: Power of variance covariate

Formula: ~fitted(.)

Parameter estimates:

```

power
0.1360297

```

Coefficients:

| | | Value | Std.Error | t-value | p-value |
|---------------------|----------------|-----------|-----------|-----------|---------|
| lA.factor(Controls) | 46615301:adult | 6.102305 | 0.0381345 | 160.02073 | 0.0000 |
| lA.factor(Controls) | 46615301:pnd11 | 6.365104 | 0.0229313 | 277.57331 | 0.0000 |
| lD.ageadult | | -2.534009 | 0.2509366 | -10.09820 | 0.0000 |
| lD.agepnd11 | | -2.824935 | 0.2475440 | -11.41185 | 0.0000 |
| lg.ageadult | | 0.513239 | 0.2328582 | 2.20408 | 0.0284 |
| lg.agepnd11 | | 0.279932 | 0.2983132 | 0.93838 | 0.3489 |
| lTr | | 0.933426 | 0.4525889 | 2.06241 | 0.0402 |

Correlation:

| | lA.f(C)46615301: 1A.(C)46615301:1 lD.gd1 lD.g11 lg.gd1 lg.g11 | | | | | |
|-----------------------------------|---|--------|-------|-------|-------|-------|
| lA.factor(Controls)46615301:pnd11 | 0.000 | | | | | |
| lD.ageadult | -0.496 | 0.000 | | | | |
| lD.agepnd11 | 0.000 | -0.527 | 0.000 | | | |
| lg.ageadult | -0.351 | 0.000 | 0.972 | 0.000 | | |
| lg.agepnd11 | 0.000 | -0.305 | 0.000 | 0.935 | 0.000 | |
| lTr | 0.000 | 0.433 | 0.000 | 0.028 | 0.000 | 0.089 |

Standardized residuals:

| Min | Q1 | Med | Q3 | Max |
|-------------|-------------|------------|------------|------------|
| -2.43371265 | -0.63031728 | 0.01431742 | 0.61150398 | 2.63801341 |

Residual standard error: 35.48174

Degrees of freedom: 267 total; 260 residual

sectionSummary The critical estimates from this analysis are listed below. They are printed with greater than usual precision, in case they are to be used in further computation. For reporting, round to two or three significant digits. BMD has units mg/kg, and times are in hours.

species RAT

mrid [1] "44254401" "44472001" "Padilla" "46615301"

Adult lD (standard error) -1.87128899635248 (0.328818947918613)

Adult BMD (95% CI) 0.153925124961350 (0.0815427642083346, 0.290558510303057)

Adult BMDL, the one-sided lower 95% CL 0.0903326998621774

Results from the comparative ChE study (MRID 46615301)

PND 11 1D (standard error) -2.82493515985183 (0.247543982143843)

PND11 BMD (95% CI) 0.0593125025362119 (0.0364293160593684, 0.0965698326966927)

PND11 BMDL, the one-sided lower 95% CL 0.0394167368397315

Adult 1D (standard error) -2.53400851219250 (0.250936572461382)

Adult BMD (95% CI) 0.079340345264903 (0.0484058189635489, 0.130044083986974)

Adult BMDL, the one-sided lower 95% CL 0.0524319898258194

Ratio of Adult to PND11 BMD (95% CI) 1.33766645938541 (0.670363310515586, 2.66922656490328)

Adult lTr (standard error) :

| Value | Std.Error |
|-------------|------------|
| -0.27691165 | 0.07985187 |

Adult Recovery Half-life (95% CI) :

| lower | est. | upper |
|-----------|-----------|-----------|
| 0.6497289 | 0.7581215 | 0.8845970 |

PND11 Recovery Half-Life (95% CI) 2.54320657218850 (1.04312316857033, 6.2005138642328)

Save everything:

```
> save.image(file = "RatRBCDR.RData")
```

Save the results for incorporating into a database:

```
> oxamyl.oral.rbc <- list(mrid = levels(dta$mrid), species = "RAT", BMDs = list(adult = list(combined =
+   "Value"), 1D.se = tTab.a["1D", "Std.Error"], BMD = exp(Ints.a["1D", "est."]), BMD.CI = exp(Ints.a
+   "upper"))), BMDL = exp(Ints90.a["1D", "lower"])), pnd11 = list(combined = list(1D = tTab.j["1D.a
+   1D.se = tTab.j["1D.agepnd11", "Std.Error"], BMD = exp(Ints.j["1D.agepnd11", "est."]), BMD.CI = ex
+   c("lower", "upper"))), BMDL = exp(Ints90.j["1D.agepnd11", "lower"]))), HalfLives = list(adul
+   rownames(tTab.a), "Value"), 1Tr.se = tTab.a[grep("^1Tr", rownames(tTab.a)), "Std.Error"], Tr = e
+   rownames(Ints.a)), "est.")), Tr.CI = exp(Ints.a[c("lower", "upper")))), pnd11 = list(lTr = tTab.j
+   lTr.se = tTab.j["lTr", "Std.Error"], Tr = exp(Ints.j["lTr", "est."]), Tr.CI = exp(Ints.j["lTr", c
> save(oxamyl.oral.rbc, file = file.path("../", "..", "01Summaries", "oxamyl.oral.rbc.RData"))
```

APPENDIX C

**Oxamyl: AChE Rat Brain Summary based on Exponent suggestion
of how to handle control values**

Dose-Time Response Modeling of Rat Brain AChE Activity: Oxamyl Gavage Dosing

September 30, 2009

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1 Preamble

Here is some code to set up the analysis: loading required libraries and datasets, and defining some functions.

First, CarbamateData loads the full dataset for this risk assessment, and causes the library DRUtils to be loaded.

```
> library(CarbamateData)
```

Set up lattice to use B&W instead of color:

```
> library(lattice)
> ltheme <- canonical.theme(color = FALSE)
> ltheme$strip.background$col <- "transparent"
> lattice.options(default.theme = ltheme)
```

Use package Hmisc for some formatting support.

```
> library(Hmisc)
```

The rat gavage data for this analysis are in AggData, PadillaData, and newdata. The following code prints out documentation for the datasets in use:

```
> printDataDoc(AggData)
```

```
-----  
Data set: AggData
```

```
Dataset creation date: Mon May 05 12:20:50 2008  
Script name: C:/EmpiricalDoseResponses/Data/getdata.R  
Script last modified: 2008-05-05 12:18:40  
sysname: Windows  
release: XP  
version: build 2600, Service Pack 2  
nodename: L2032JPVILLANU  
machine: x86  
login: pvillanu  
user: pvillanu
```

```
> printDataDoc(PadillaData)
```

```
Data set: PadillaData
```

```
Dataset creation date: Mon May 05 12:20:58 2008  
Script name: C:/EmpiricalDoseResponses/Data/getdata.R  
Script last modified: 2008-05-05 12:18:40  
sysname: Windows  
release: XP  
version: build 2600, Service Pack 2  
nodename: L2032JPVILLANU  
machine: x86  
login: pvillanu  
user: pvillanu
```

```
> printDataDoc(newdata)
```

```
Data set: newdata
```

```
Dataset creation date: Mon May 05 12:20:58 2008  
Script name: C:/EmpiricalDoseResponses/Data/getdata.R  
Script last modified: 2008-05-05 12:18:40  
sysname: Windows  
release: XP  
version: build 2600, Service Pack 2  
nodename: L2032JPVILLANU  
machine: x86  
login: pvillanu  
user: pvillanu
```

The following function turns out to be quite useful on subsetted dataframes. It just eliminates unused levels of all factors in the data frame:

```
> CleanUp <- function(x) {  
+   for (nm in names(x)) {  
+     if (is.factor(x[, nm]))
```

```

+           x[, nm] <- factor(x[, nm])
+
+       }
+
+   x
+
}

```

To get starting values, we often have to extract values from a previously fit model. The following function simplifies that. The argument what is a regular expression:

```

> getParms <- function(what, Par) {
+   Par[grep(what, names(Par))]
+ }

```

This script is for modeling the dose-time response for rat brain via gavage dosing. It includes acute, subchronic, and chronic studies.

All the data used for this DR model are in AggData and in PadillaData. The oxamyl data need to be extracted from both data sets, then several variables ($n = 1$, $sd = 0$, $tmonstdy = 1$, $mrid = "Padilla"$, $cheact = Brain.R$) added to the Padilla dataset. To keep the response scale similar across studies, Padilla's values for cheact need to be divided by 500. Finally the two datasets are combined, and all activity levels and their standard deviation rescaled by ten (this seems to make it easier).

These are all the names used for the brain sections we want from AggData:

```
> BrainSections <- levels(AggData$sctn)[grep("(^BRAIN)|(^WHOLEBRAIN)|(LEFT HEMISPHERE)|(HALFBRAIN)", le
```

Now, set up the analysis dataset.

```

> dta <- CleanUp(subset(AggData, chemical %in% "OXAMYL" & species %in% "RAT" & dsmttd %in% "GAVAGE" & sc
+   !is.na(cheact) & (n == 1 | !is.na(sd)), select = c("cheact", "sd", "n", "dose", "tmpstds", "sex",
> tdt <- with(dta, PhonyDF(dose, n, cheact, sd, "dose", "cheact", Avals = dta[, c("tmpstds", "sex", "m
> tdt$age <- factor(rep("adult", nrow(tdt)), levels = c("adult", "pnd11"))
> tdt$type <- factor(c(`44254401` = "doseresponse", `44420301` = "doseresponse", `44472001` = "timecou
> Pdta <- CleanUp(subset(PadillaData, chemical %in% "oxamyl", select = c("dose", "brain.R", "TMPSTDS"))
> names(Pdta) <- c("dose", "cheact", "tmpstds")
> Pdta$sex <- factor(rep("M", nrow(Pdta)), levels = c("F", "M"))
> Pdta$age <- factor(rep("adult", nrow(Pdta)), levels = c("adult", "pnd11"))
> Pdta$mrid <- factor(rep("padilla", nrow(Pdta)))
> Pdta$cheact <- Pdta$cheact/500
> Pdta$type <- factor(ifelse(abs(Pdta$tmpstds - 2/3) < 0.001, "doseresponse", "timecourse"))
> dta2 <- CleanUp(subset(newdata, chemical %in% "Oxamyl", select = c("dose", "brain", "time", "age", "s
> names(dta2) <- c("dose", "cheact", "tmpstds", "age", "sex", "mrid")
> dta2$tmpstds <- dta2$tmpstds/60
> dta2$age <- factor(ifelse(dta2$age > 40, "adult", "pnd11"))
> dta2$type <- factor(c(rep("timecourse", 100), rep("doseresponse", nrow(dta2) - 100)))
> dta2 <- dta2[!is.na(dta2$cheact), ]
> dta <- rbind(tdt, Pdta[, names(tdt)], dta2[, names(tdt)])

```

Summary of the relevant variables in this dataset:

```
> by(dta, dta$mrid, summary)
```

| dta\$mrid: 44254401 | dose | cheact | tmpstds | sex | mrid | age | type |
|---------------------|----------------|---------------|---------|--------------|-----------|------------------|------|
| Min. :0.0000 | Min. : 2.946 | Min. : 1.0 | F:120 | 44254401:239 | adult:239 | doseresponse:239 | |
| 1st Qu.:0.0500 | 1st Qu.:10.436 | 1st Qu.: 1.0 | M:119 | 44472001: 0 | pnd11: 0 | timecourse : 0 | |
| Median :0.1000 | Median :11.326 | Median : 24.0 | | padilla : 0 | | | |
| Mean :0.6757 | Mean :10.473 | Mean :128.8 | | 46615301: 0 | | | |
| 3rd Qu.:1.0000 | 3rd Qu.:12.037 | 3rd Qu.:360.0 | | | | | |
| Max. :2.0000 | Max. :14.131 | Max. :360.0 | | | | | |

dta\$mrid: 44472001

| dose | cheact | tmpstds | sex | mrid | age | type |
|-------------|----------------|---------------|------|--------------|-----------|-----------------|
| Min. :0.0 | Min. : 5.035 | Min. :0.500 | F:80 | 44254401: 0 | adult:160 | doseresponse: 0 |
| 1st Qu.:0.0 | 1st Qu.:11.063 | 1st Qu.:1.625 | M:80 | 44472001:160 | pnd11: 0 | timecourse :160 |
| Median :0.5 | Median :11.727 | Median :2.500 | | padilla : 0 | | |
| Mean :0.5 | Mean :11.146 | Mean :2.375 | | 46615301: 0 | | |
| 3rd Qu.:1.0 | 3rd Qu.:12.319 | 3rd Qu.:3.250 | | | | |
| Max. :1.0 | Max. :13.908 | Max. :4.000 | | | | |

dta\$mrid: padilla

| dose | cheact | tmpstds | sex | mrid | age | type |
|----------------|----------------|-----------------|------|-------------|----------|-----------------|
| Min. :0.0000 | Min. : 3.879 | Min. : 0.5000 | F: 0 | 44254401: 0 | adult:59 | doseresponse:30 |
| 1st Qu.:0.0833 | 1st Qu.: 7.307 | 1st Qu.: 0.6667 | M:59 | 44472001: 0 | pnd11: 0 | timecourse :29 |
| Median :1.0000 | Median :10.142 | Median : 0.6667 | | padilla :59 | | |
| Mean :0.6751 | Mean : 9.660 | Mean : 3.0847 | | 46615301: 0 | | |
| 3rd Qu.:1.0000 | 3rd Qu.:12.363 | 3rd Qu.: 1.5000 | | | | |
| Max. :1.5000 | Max. :14.670 | Max. :24.0000 | | | | |

dta\$mrid: 46615301

| dose | cheact | tmpstds | sex | mrid | age | type |
|----------------|----------------|---------------|-------|--------------|-----------|------------------|
| Min. :0.0000 | Min. : 3.400 | Min. :0.500 | F:180 | 44254401: 0 | adult:157 | doseresponse:257 |
| 1st Qu.:0.0750 | 1st Qu.: 5.400 | 1st Qu.:0.500 | M:175 | 44472001: 0 | pnd11:198 | timecourse : 98 |
| Median :0.1000 | Median : 6.600 | Median :0.500 | | padilla : 0 | | |
| Mean :0.1121 | Mean : 7.213 | Mean : 1.818 | | 46615301:355 | | |
| 3rd Qu.:0.1500 | 3rd Qu.: 9.400 | 3rd Qu.:4.000 | | | | |
| Max. :0.2500 | Max. :11.700 | Max. :6.000 | | | | |

> with(dta, print(table(dose, tmpstds, interaction(mrid, age, sex, drop = TRUE, sep = ":")), zero.print
, , = 44254401:adult:F

tmpstds

| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
|--------|-----|--------------------|----|-----|---|---|---|----|----|-----|
| 0 | . | . | 10 | . | . | . | . | 10 | 10 | |
| 0.0666 | . | . | . | . | . | . | . | . | . | |
| 0.075 | . | . | . | . | . | . | . | . | . | |
| 0.1 | . | . | 10 | . | . | . | . | 10 | 10 | |
| 0.125 | . | . | . | . | . | . | . | . | . | |
| 0.15 | . | . | . | . | . | . | . | . | . | |
| 0.2 | . | . | . | . | . | . | . | . | . | |
| 0.25 | . | . | . | . | . | . | . | . | . | |
| 0.5 | . | . | . | . | . | . | . | . | . | |
| 0.75 | . | . | 10 | . | . | . | . | 10 | 10 | |
| 1 | . | . | . | . | . | . | . | . | . | |
| 1.5 | . | . | 10 | . | . | . | . | 10 | 10 | |
| 2 | . | . | . | . | . | . | . | . | . | |

, , = 44472001:adult:F

tmpstds

| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
|--------|-----|--------------------|---|-----|----|----|---|---|----|-----|
| 0 | 10 | . | . | 10 | 10 | 10 | . | . | . | |
| 0.0666 | . | . | . | . | . | . | . | . | . | |
| 0.075 | . | . | . | . | . | . | . | . | . | |

| | | | | | | | | | |
|-------|----|---|---|----|----|----|---|---|---|
| 0.1 | . | . | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . |
| 1 | 10 | . | . | 10 | 10 | 10 | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . |

, , = 46615301:adult:F

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|----|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |
| 0.1 | . | . | . | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . | . |
| 0.15 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.2 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.25 | 10 | . | . | . | . | 10 | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | . | . | . | . | . | . | . | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = 46615301:pnd11:F

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|---|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | 5 | 5 | 5 | 5 | 5 | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | 10 | . | . | . | . | . | . | . | . | . |
| 0.1 | 15 | . | 5 | 5 | 5 | 5 | 5 | . | . | . |
| 0.125 | 10 | . | . | . | . | . | . | . | . | . |
| 0.15 | 10 | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | . | . | . | . | . | . | . | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = 44254401:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|----|-----|---|---|---|----|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | . | . | 10 | . | . | . | . | 10 | 10 | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |

| | | | | | | | | | |
|-------|---|---|----|---|---|---|---|----|----|
| 0.1 | . | . | 10 | . | . | . | . | 10 | 10 |
| 0.125 | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . |
| 1 | . | . | 10 | . | . | . | . | 10 | 10 |
| 1.5 | . | . | . | . | . | . | . | . | . |
| 2 | . | . | 10 | . | . | . | . | 9 | 10 |

, , = 44472001:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|----|----|----|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | . | . | 10 | 10 | 10 | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |
| 0.1 | . | . | . | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | . | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | 10 | . | . | . | 10 | 10 | 10 | . | . | . |
| 1.5 | . | . | . | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = padilla:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|---|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 1 | . | 5 | 1 | 1 | . | . | 1 | . | 1 |
| 0.0666 | . | . | 5 | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |
| 0.1 | . | . | 5 | . | . | . | . | . | . | . |
| 0.125 | . | . | . | . | . | . | . | . | . | . |
| 0.15 | . | . | . | . | . | . | . | . | . | . |
| 0.2 | . | . | . | . | . | . | . | . | . | . |
| 0.25 | . | . | . | . | . | . | . | . | . | . |
| 0.5 | . | . | 5 | . | . | . | . | . | . | . |
| 0.75 | . | . | . | . | . | . | . | . | . | . |
| 1 | 5 | . | 5 | 5 | . | . | 5 | . | 4 | . |
| 1.5 | . | . | 5 | . | . | . | . | . | . | . |
| 2 | . | . | . | . | . | . | . | . | . | . |

, , = 46615301:adult:M

| tmpstds | | | | | | | | | | |
|---------|-----|--------------------|---|-----|---|---|---|---|----|-----|
| dose | 0.5 | 0.6666666666666667 | 1 | 1.5 | 2 | 3 | 4 | 6 | 24 | 360 |
| 0 | 10 | . | . | . | . | . | 7 | . | . | . |
| 0.0666 | . | . | . | . | . | . | . | . | . | . |
| 0.075 | . | . | . | . | . | . | . | . | . | . |

```

0.1
0.125
0.15 10
0.2 10
0.25 10
0.5
0.75
1
1.5
2

, , = 46615301:pnd11:M

      tmpstds
dose   0.5 0.6666666666666667  1 1.5  2  3  4  6 24 360
  0    10          . 5  . 5  . 5  .  .
  0.0666
  0.075 10
  0.1   14          . 5  5  4  5  5  5  .
  0.125 10
  0.15 10
  0.2
  0.25
  0.5
  0.75
  1
  1.5
  2

```

Padilla's data are from an acute study, with multiple doses at one time point, and multiple timepoints for 1 mg/kg. Mrids 44254401, 44420301, and 44472001 are acute studies. The only dose at which there is a useful time course in adults is at 1 mg/kg, in both the Padilla study and 44472001. The new study 46615301 has a time course study in pnd11 animals conducted at 0.1 mg/kg. The earliest time point in any study is 0.5 hour after dosing, and all the dose-response data sets include this time point. Some also include later (some, much later) time points.

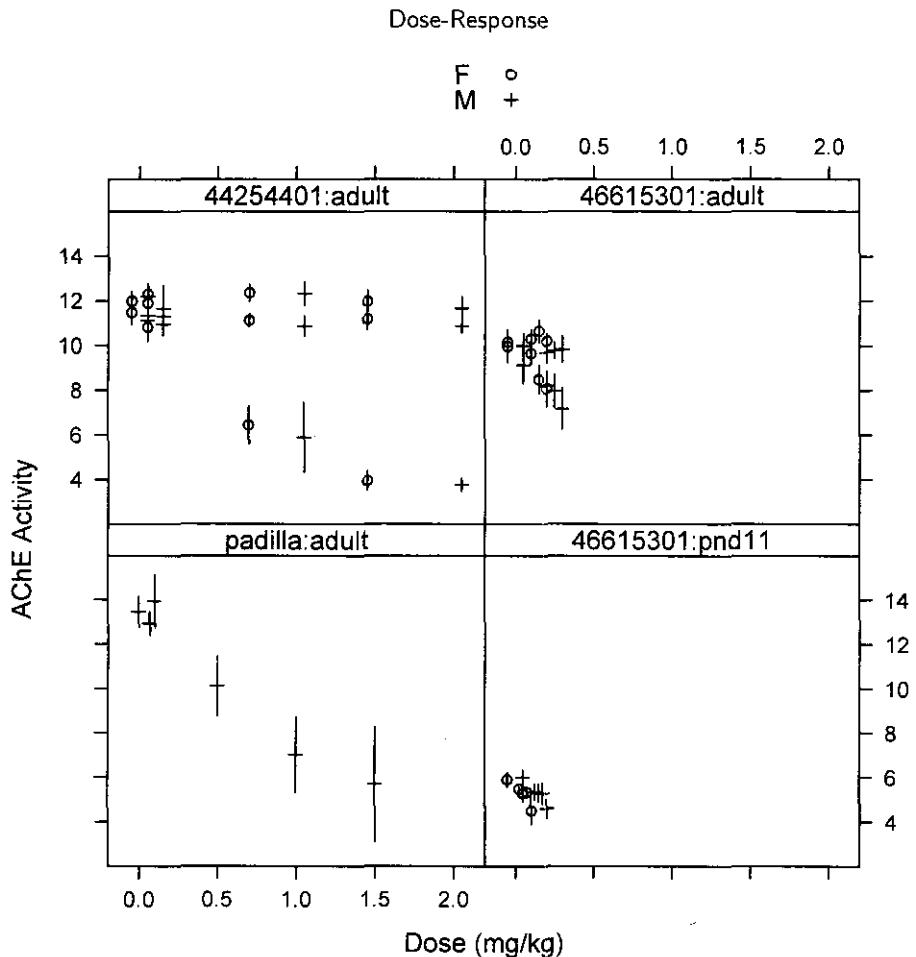
Create some new factors, for splitting up the background parameters and allowing groups to have different variances.

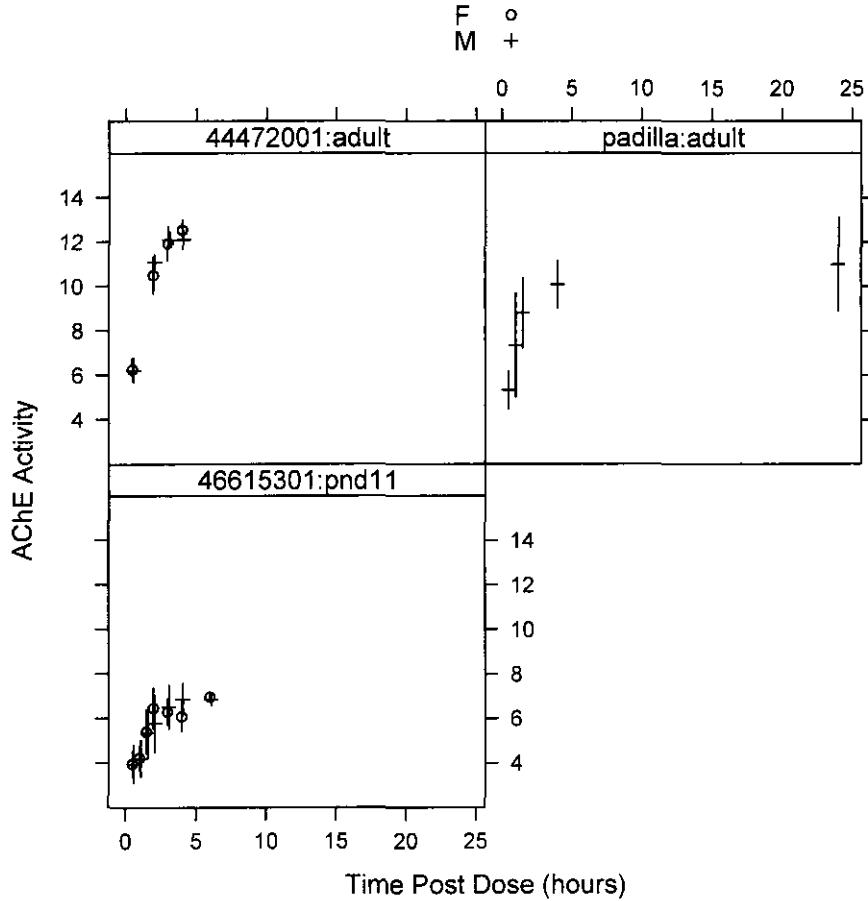
```
> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE, sep = ":"))  
> dta$mridXsexXtmpstds <- with(dta, interaction(mrid, sex, tmpstds, drop = TRUE, sep = ":"))
```

2 Dose-Response Modeling

2.1 A Quick Look at the Data

```
> dta$cells <- with(dta, interaction(mrid, age, sex, dose, tmpstds, type, drop = TRUE, sep = ":"))  
> tmp <- tapply(dta$cheact, dta$cells, function(x) c(mean(x), sd(x), length(x)))  
> nm <- names(tmp)  
> tmp <- matrix(unlist(tmp), ncol = 3, byrow = TRUE)  
> rownames(tmp) <- nm  
> nmmx <- matrix(unlist(strsplit(nm, ":")), ncol = 6, byrow = TRUE)  
> dta.summ <- data.frame(che = tmp[, 1], che.lower = ifelse(tmp[, 3] > 1, tmp[, 1] + qt(0.025, tmp[, 3]  
+ 3)], NA, che.upper = ifelse(tmp[, 3] > 1, tmp[, 1] + qt(0.975, tmp[, 3] - 1) * tmp[, 2]/sqrt(tmp[,  
+ 1])), age = factor(nmmx[, 2]), sex = factor(nmmx[, 3]), dose = as.numeric(nmmx[, 4]), tmpstds = as.  
+ 5], type = factor(nmmx[, 6]))
```





Apparently, the response is already increasing at the 30 minute time point, so the time to peak effect is not greater than 30 minutes for brain AChE inhibition.

2.2 strategy

There are two sets of goals for this analysis. For all the adult data, we need an estimate for the dose that would result in 10% brain AChE inhibition (the benchmark dose, BMD), as well as an estimate of the half-life of recovery from peak inhibition. For the study that contains both adult and pnd11 animals, we want an estimate of age-specific BMD, and the ratio of adult to pnd11 BMD, and the age-specific half-life. Thus, two analyses are required: one of all the adult data, and the other of all the data from MRID 46615301.

Each analysis will proceed in a similar fashion. First, how do we handle the controls? There are typically controls at each time point for studies of recovery. If the control values are homogeneous, then it will simplify the analysis to fit a common control value across all time points for each study. If the control values are heterogeneous, then we assume that the concurrent control is the appropriate point of comparison for the activity in a dose group, so a factor needs to be set up to allow control values to vary across time points. The EPA study has a single animal per time point in the time-course study, so the critical questions for that study will be:

- is there a time-related trend among the controls?
- is the variance among the time-course controls significantly greater than that among the dose-response controls?
- does the mean time-course control value differ significantly from the mean dose-response control value.

In 44472001, there is a control group for each time. For this study the questions will be, for each sex: do the two time-course controls differ?

In the pnd11 animals of 46615301, there are concurrent controls for only some of the time points. Thus, in addition to determining whether the controls are heterogeneous across time, if the answer is "yes", then we need to determine how to set a control level for each time point.

In the registrant-submitted studies, we will maintain differences between sex and age, at the least.

The remaining dose-response parameters are initially allowed to vary among MRID and sex (and age, when appropriate), to the extent possible for the design (in particular, the recovery half-life can only be estimated in studies where there is a recovery component). Once a model is fit, Wald type tests are used to collapse the initial richly parameterized model to a simpler one; for example, if the data do not support allowing Ig to vary among studies or sexes, fitting a simpler parameterization.

The dose-response parameters, ID , Ig , and tz may not be estimable with the data at hand. In particular, it is generally not possible to estimate tz , unless doses are so great that the response has reached its asymptotic value. In the course of getting initial values for these parameters, if it is clear that tz cannot be estimated, it is fixed at -10, which sets the maximum possible inhibition level to be nearly 100%.

2.3 How Heterogeneous are the Time Course Controls?

The EPA dataset has just one animal per time point in the time course control group. We can do tests there to determine whether there is any additional variability among times: regression of response on time among the controls to look for trends, and comparison of the variance among times to the variance among the control animals from the dose-response portion of the study. We do these tests here. First, regression of the responses on time:

```
> with(subset(dta, mrnid == "padilla" & dose == 0 & type == "timecourse"), {
+   print(summary(lm(cheact ~ tmpstds)))
+ })
```

Call:

```
lm(formula = cheact ~ tmpstds)
```

Residuals:

| | 1 | 2 | 3 | 4 | 5 |
|----------|---------|----------|---------|----------|---|
| -0.63887 | 0.71780 | -0.10253 | 0.04055 | -0.01695 | |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|--------------|
| (Intercept) | 10.17109 | 0.30352 | 33.511 | 5.84e-05 *** |
| tmpstds | 0.04875 | 0.02781 | 1.753 | 0.178 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 . 1

Residual standard error: 0.5585 on 3 degrees of freedom
 Multiple R-squared: 0.506, Adjusted R-squared: 0.3414
 F-statistic: 3.073 on 1 and 3 DF, p-value: 0.1779

The test for trend is the significance of the coefficient for tmpstds. The P-value is 0.178, so there is no evidence for a trend. Now, compare the variances among the time course controls with the dose-response controls:

```
> with(subset(dta, mrnid == "padilla" & dose == 0), {
+   tc <- cheact[type == "timecourse"]
+   dr <- cheact[type == "doseresponse"]
+   var.test(tc, dr)
+ })
```

F test to compare two variances

```
data: tc and dr
F = 1.5082, num df = 4, denom df = 4, p-value = 0.7002
alternative hypothesis: true ratio of variances is not equal to 1
95 percent confidence interval:
0.1570307 14.4856120
sample estimates:
ratio of variances
1.508206
```

There is no reason to think there is added variability among the time-course controls. Finally, are the two control groups different from each other?

```
> with(subset(dta, mrid == "padilla" & dose == 0), {
+   tc <- cheact[type == "timecourse"]
+   dr <- cheact[type == "doseresponse"]
+   t.test(tc, dr)
+ })
```

Welch Two Sample t-test

```
data: tc and dr
t = -7.5155, df = 7.685, p-value = 8.422e-05
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-3.904777 -2.061094
sample estimates:
mean of x mean of y
10.47337 13.45630
```

The time course and dose-response controls differ from each other, so use a separate control value for the dose-response and time-course portions of that study (that is, use a two values of *IA* for the entire EPA dataset).

Next, how heterogeneous are the controls in 44472001? We test for both trend and heterogeneity:

```
> with(subset(dta, mrid == "44472001" & dose == 0), {
+   print(summary(lm(cheact ~ sex + tmpstds + tmpstds:sex)))
+   print(summary(lm(cheact ~ sex + tmpstds)))
+   out1 <- lm(cheact ~ sex * factor(tmpstds))
+   out2 <- lm(cheact ~ sex + factor(tmpstds))
+   print(anova(out1, out2, test = "F"))
+ })
```

Call:
`lm(formula = cheact ~ sex + tmpstds + tmpstds:sex)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -1.15523 | -0.41188 | -0.04461 | 0.31723 | 2.14394 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|------------|
| (Intercept) | 11.89364 | 0.20847 | 57.051 | <2e-16 *** |
| sexM | -0.58234 | 0.29483 | -1.975 | 0.0519 . |
| tmpstds | 0.13215 | 0.07709 | 1.714 | 0.0906 . |

```

sexM:tmpstds  0.01888    0.10903    0.173    0.8630
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   .
Residual standard error: 0.6304 on 76 degrees of freedom
Multiple R-squared:  0.219,      Adjusted R-squared:  0.1882
F-statistic: 7.104 on 3 and 76 DF,  p-value: 0.0002857

```

Call:
`lm(formula = cheact ~ sex + tmpstds)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -1.13989 | -0.40095 | -0.03753 | 0.31310 | 2.14984 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|--------------|
| (Intercept) | 11.87123 | 0.16237 | 73.114 | < 2e-16 *** |
| sexM | -0.53750 | 0.14008 | -3.837 | 0.000253 *** |
| tmpstds | 0.14159 | 0.05417 | 2.614 | 0.010764 * |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 .

Residual standard error: 0.6265 on 77 degrees of freedom
Multiple R-squared: 0.2187, Adjusted R-squared: 0.1984
F-statistic: 10.78 on 2 and 77 DF, p-value: 7.469e-05

Analysis of Variance Table

```

Model 1: cheact ~ sex * factor(tmpstds)
Model 2: cheact ~ sex + factor(tmpstds)
  Res.Df   RSS Df Sum of Sq   F Pr(>F)
  1     72 25.0959
  2     75 28.6143 -3   -3.5184 3.3647 0.02321 *
---

```

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 .

There is a significantly increasing linear trend that does not differ between the sexes, and some evidence of interaction between time and sex in the variability of the means. For this study, we keep a separate control value for each sex and time.

Finally, the controls for the pnd11 animals of 46615301. We combine the timecourse and dose-response portions, because the 0.5 hour control timepoint is just in the dose-response portion of the study.

```

> with(subset(dta, mrid == "46615301" & age == "pnd11" & dose == 0), {
+   print(summary(lm(cheact ~ sex + tmpstds + tmpstds:sex)))
+   print(summary(lm(cheact ~ sex + tmpstds)))
+   out1 <- lm(cheact ~ sex * factor(tmpstds))
+   out2 <- lm(cheact ~ sex + factor(tmpstds))
+   print(anova(out1, out2, test = "F"))
+   print(summary(out2))
+ })

```

Call:
`lm(formula = cheact ~ sex + tmpstds + tmpstds:sex)`

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|----------|----------|---------|---------|---------|
| | -1.67931 | -0.33397 | 0.08126 | 0.33989 | 1.09954 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|--------------|----------|------------|---------|-------------|
| (Intercept) | 5.50690 | 0.18538 | 29.706 | < 2e-16 *** |
| sexM | 0.25126 | 0.26217 | 0.958 | 0.34287 |
| tmpstds | 0.30069 | 0.08940 | 3.363 | 0.00156 ** |
| sexM:tmpstds | -0.07954 | 0.12643 | -0.629 | 0.53238 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1

Residual standard error: 0.5896 on 46 degrees of freedom

Multiple R-squared: 0.2811, Adjusted R-squared: 0.2342

F-statistic: 5.995 on 3 and 46 DF, p-value: 0.001548

Call:

lm(formula = cheact ~ sex + tmpstds)

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|---------|---------|--------|--------|--------|
| | -1.6554 | -0.3853 | 0.0804 | 0.3560 | 1.0836 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|-------------|----------|------------|---------|--------------|
| (Intercept) | 5.57053 | 0.15436 | 36.089 | < 2e-16 *** |
| sexM | 0.12400 | 0.16570 | 0.748 | 0.457973 |
| tmpstds | 0.26092 | 0.06281 | 4.154 | 0.000137 *** |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1

Residual standard error: 0.5858 on 47 degrees of freedom

Multiple R-squared: 0.2749, Adjusted R-squared: 0.244

F-statistic: 8.909 on 2 and 47 DF, p-value: 0.0005241

Analysis of Variance Table

| Model 1: cheact ~ sex * factor(tmpstds) |
|---|
| Model 2: cheact ~ sex + factor(tmpstds) |
| Res.Df RSS Df Sum of Sq F Pr(>F) |
| 1 42 8.9880 |
| 2 45 9.6788 -3 -0.6908 1.076 0.3696 |

Call:

lm(formula = cheact ~ sex + factor(tmpstds))

Residuals:

| | Min | 1Q | Median | 3Q | Max |
|--|---------|---------|---------|--------|--------|
| | -1.0880 | -0.2495 | -0.0200 | 0.2995 | 0.8980 |

Coefficients:

```

          Estimate Std. Error t value Pr(>|t|)
(Intercept)      5.8680    0.1227  47.823 < 2e-16 ***
sexM            0.1240    0.1312   0.945  0.349551
factor(tmpstds)1 -0.6900    0.1796  -3.841  0.000381 ***
factor(tmpstds)2  0.6200    0.1796   3.452  0.001223 **
factor(tmpstds)4  0.6700    0.1796   3.730  0.000534 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1 .

```

Residual standard error: 0.4638 on 45 degrees of freedom
 Multiple R-squared: 0.5649, Adjusted R-squared: 0.5262
 F-statistic: 14.61 on 4 and 45 DF, p-value: 1.012e-07

Do the 0.1 mg/kg time course group at 0.5 hour differ from the 0.1 mg/kg dose-response group at 0.5 hour? If not, assign the same control group at that time to both groups:

```

> with(subset(dta, mrid == "46615301" & age == "pnd11" & dose == 0.1), {
+   print(summary(lm(cheact ~ type * sex)))
+   print(summary(lm(cheact ~ type + sex)))
+ })

```

Call:
`lm(formula = cheact ~ type * sex)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -2.2939 | -0.8418 | 0.1250 | 0.9070 | 1.9061 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|---------------------|----------|------------|---------|------------|
| (Intercept) | 5.26000 | 0.35486 | 14.823 | <2e-16 *** |
| typetimecourse | 0.36571 | 0.40238 | 0.909 | 0.366 |
| sexM | 0.03000 | 0.50185 | 0.060 | 0.952 |
| typetimecourse:sexM | 0.03823 | 0.57096 | 0.067 | 0.947 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 .

Residual standard error: 1.122 on 84 degrees of freedom
 Multiple R-squared: 0.02183, Adjusted R-squared: -0.01311
 F-statistic: 0.6248 on 3 and 84 DF, p-value: 0.601

Call:
`lm(formula = cheact ~ type + sex)`

Residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -2.2895 | -0.8486 | 0.1250 | 0.9105 | 1.9105 |

Coefficients:

| | Estimate | Std. Error | t value | Pr(> t) |
|----------------|----------|------------|---------|------------|
| (Intercept) | 5.24523 | 0.27637 | 18.979 | <2e-16 *** |
| typetimecourse | 0.38470 | 0.28380 | 1.356 | 0.179 |
| sexM | 0.05953 | 0.23792 | 0.250 | 0.803 |

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 S S 1

Residual standard error: 1.116 on 85 degrees of freedom
 Multiple R-squared: 0.02177, Adjusted R-squared: ~0.001242
 F-statistic: 0.946 on 2 and 85 DF, p-value: 0.3923

The controls are heterogeneous, with an upward trend with increasing time that does not differ between the sexes. The first two outputs copied above tell that story. However, this does not tell the whole story. When we treat time post dose as a factor, we see again that the sexes do not differ, but the means do not change linearly with time. In the last output above, the (Intercept) term is the mean for the 0.5 hour females, and their terms factor(tmpstds)1, etc. are differences between the (in this case) 1 hour time point and the 0.5 hour time point. There is a significant, roughly 10%, drop from 0.5 hour to 1 hour, then, at 2 and 4 hours, the means are roughly 10% greater than the 0.5 hour mean. All these differences are individually significant; that is, the differences are much greater than would be expected from the sampling variability.

The following code sets up a factor to handle the control values we need:

```
> dta$Controls <- with(dta, interaction(mrid, sex, age, type, tmpstds, drop = TRUE, sep = ":"))  

> lvls <- levels(dta$Controls)  

> lvls[grep("^padilla.*timecourse", lvls)] <- "padilla:timecourse"  

> lvls[grep("^padilla.*doseresponse", lvls)] <- "padilla:doseresponse"  

> lvls <- sub("(46615301:(F/M):pnd11:)timecourse(:0.5)", "\\\doseresponse\\3", lvls)  

> levels(dta$Controls) <- lvls
```

2.4 Levels for tz, lg, 1D, and 1Tr

The log benchmark dose, 1D, will have a random component (among mrids) in the final analysis, and in addition, will take on different values by sex and age. This may be collapsed after testing for differences between sexes, and contrasts between ages will be calculated. Since only the dose-response portions of the data provide information about 1D, we need to pair the one time-course-only mrid (44472001) with a dose-response mrid. This will be (somewhat arbitrarily) 44254401

Whether we can estimate values for lg and/or tz at all depends critically on the experimental design. In particular, unless the doses are great enough that inhibition approaches a plateau, tz will not be well identified. If there are no doses low enough to determine a low-dose plateau, lg will be governed by the shape of the dose-response curve at higher doses, as the response levels out with increasing dose. In that case, experience shows that lg and tz are strongly confounded. The plots of the adult dose-response data above suggest that lg may be positive, and that the dose-response *may* be beginning to level off at the higher doses. There are certainly not enough data to estimate separate values of lg and tz for each dataset, but we may be able to borrow across datasets. So, we will try fitting gender-specific values for these two parameters, pooling across all adult datasets. When we compare adult to pnd11 values in 46615301, we will just set tz = -10, as there is clearly no way to estimate that parameter from these data, as the doses in that study are too low to allow the response to even begin to plateau.

The (log) half-life parameter, 1Tr, is estimable in adults from two datasets. Rather than assign dose-response datasets to one or the other time-course dataset, we just estimate a pooled value over the whole set of data for each sex.

Finally, estimate a separate variance constant for each study X sex combination. Setup of factors to allow the above:

```
> dta$mrid2 <- dta$mrid  

> lvls <- levels(dta$mrid)  

> lvls[lvls == "44472001"] <- "44254401"  

> levels(dta$mrid2) <- lvls  

> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE, sep = ":"))
```

3 Adult Dose-Response Modeling

3.1 strategy

Use the model with simple exponential recovery (`tcmfn4()`). It looks as if the time to peak effect for all these chemicals is likely to be less than a half-hour, so the exponential recovery model is probably indistinguishable from the one with the more complex time course.

Fitting the model will follow these steps:

1. First, use `GetInitialValues()` to get starting values for the model against these data, and determine whether we can estimate `lg` and `tz` of the dose-response parameters.
2. Next, fit `tcmfn4()` using the parameterizations determined in the previous step. Since there are three data sets, use `nlme()`, with a random effect for `mrid`. Both time course studies were done at about the same dose, so fit a single value for `lTr` (initially, for each sex and `mrid`).

Set up an adult-only dataset:

```
> dta.a <- CleanUp(subset(dta, age == "adult"))
```

3.2 Initial Values

Save the initial values so that we do not need to go through all this to re-run the analysis. Also, set the argument `delta` to 0.5, the earliest non-zero time point.

```
> formals(tcmfn4)$delta <- min(dta$tmpstds[dta$tmpstds > 0])
> initfile <- paste("initvals-brain-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+   lA.start <- lm(I(log(cheact)) ~ Controls - 1, data = CleanUp(subset(dta.a, dose %in% 0)))
+   Start <- c(coef(lA.start), rep(log(0.2), nlevels(dta.a$sex)), rep(log(0.15), nlevels(dta.a$mridXs)
+     nlevels(dta.a$sex)), rep(log(1.5), nlevels(dta.a$sex)))
+   init1 <- GetInitialValues(cheact ~ tcmfn4(dose, tmpstds, lA = lA, tz = tz, lD = lD, lg = lg, lTr
+     params = list(lA ~ Controls - 1, tz ~ sex - 1, lD ~ mridXsex - 1, lg ~ sex - 1, lTr ~ sex - 1
+     weights = varComb(varIdent(form = ~1 | mridXsex), varPower(value = 1)))
+   save(init1, file = initfile)
+ } else load(initfile)
> tmp <- t(init1$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:5], digits = 2)
```

| | [,1] | [,2] | [,3] | [,4] | [,5] |
|-----------------------|-------|-------|------|------|------|
| CondIndex | 45.74 | 22.60 | 7.85 | 6.71 | 4.45 |
| mu | 0.04 | 0.08 | 0.24 | 0.28 | 0.43 |
| tz.sexF | 0.01 | 0.00 | 0.91 | 0.00 | 0.00 |
| tz.sexM | 0.00 | 0.28 | 0.00 | 0.57 | 0.00 |
| lD.mridXsex44254401:F | 0.99 | 0.00 | 0.00 | 0.00 | 0.00 |
| lD.mridXsex44472001:F | 0.99 | 0.00 | 0.00 | 0.00 | 0.00 |
| lD.mridXsex46615301:F | 0.74 | 0.00 | 0.00 | 0.00 | 0.00 |
| lD.mridXsex44254401:M | 0.00 | 0.89 | 0.00 | 0.01 | 0.00 |
| lD.mridXsex44472001:M | 0.00 | 0.89 | 0.00 | 0.00 | 0.00 |
| lD.mridXsexpadilla:M | 0.00 | 0.97 | 0.00 | 0.01 | 0.00 |
| lD.mridXsex46615301:M | 0.00 | 0.19 | 0.00 | 0.00 | 0.73 |
| lg.sexF | 1.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| lg.sexM | 0.00 | 0.99 | 0.00 | 0.00 | 0.00 |
| lTr.sexF | 0.00 | 0.00 | 0.96 | 0.00 | 0.00 |
| lTr.sexM | 0.00 | 0.02 | 0.00 | 0.91 | 0.00 |

```

> init1$start$beta

1A.Controls46615301:F:adult:doseresponse:0.5 1A.Controls46615301:M:adult:doseresponse:0.5 1A.Controls-
                                         2.3050864                               2.2203977
1A.Controls44472001:M:adult:timecourse:0.5          1A.Controlspadilla:timecourse
                                         2.4035198                               2.3809061
1A.Controls44254401:F:adult:doseresponse:1 1A.Controls44254401:M:adult:doseresponse:1 1A.Contro-
                                         2.4772793                               2.4123406
1A.Controls44472001:M:adult:timecourse:2 1A.Controls44472001:F:adult:timecourse:3 1A.Contro-
                                         2.5107231                               2.5281572
1A.Controls46615301:F:adult:doseresponse:4 1A.Controls46615301:M:adult:doseresponse:4 1A.Contro-
                                         2.3403826                               2.2917047
1A.Controls44472001:M:adult:timecourse:4 1A.Controls44254401:F:adult:doseresponse:24 1A.Controls4-
                                         2.4895579                               2.4973288
1A.Controls44254401:F:adult:doseresponse:360 1A.Controls44254401:M:adult:doseresponse:360 1A.Controls-
                                         2.4121117                               2.4076197
                                         tz.sexM
                                         -38.5157680
                                         1D.mridXsex46615301:F
                                         -1.6905656
                                         1D.mridXsexpadilla:M
                                         -1.4155363
                                         lg.sexM
                                         0.2759736
                                         1D.mridXsex44254401:F
                                         -1.2329021
                                         1D.mridXsex44254401:M
                                         -1.8938615
                                         1D.mridXsex46615301:M
                                         -1.9778174
                                         lTr.sexF
                                         -0.1659953

```

The above shows the results of a redundancy analysis. tz is pushed by the optimization to very small values (about -33), which generally results in numerical problems, and is consistent with essentially no positive horizontal asymptote. So, fix tz to -10, and re-estimate:

```

> formals(tcmlfn4)$delta <- min(dta$tmpstds[dta$tmpstds > 0])
> formals(tcmlfn4)$tz <- -10
> initfile <- paste("initvals-brain-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+   Start <- init1$start$beta
+   Start <- Start[-grep("tz", names(Start))]
+   init2 <- GetInitialValues(cheact ~ tcmlfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, lTr = lTr), d-
+     Controls - 1, 1D ~ mridXsex - 1, lg ~ sex - 1, lTr ~ sex - 1), start = Start, weights = varCo-
+     mridXsex), varPower(value = 1))
+   save(init2, file = initfile)
+ } else load(initfile)
> tmp <- t(init2$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^1A", rownames(tmp)), ]
> round(tmp[, 1:5], digits = 2)

                                         [,1]  [,2]  [,3]  [,4]  [,5]
CondIndex           42.31 17.55 4.04 3.84 3.52
mu                 0.04  0.10  0.43  0.45  0.49
1D.mridXsex44254401:F 0.99  0.00  0.00  0.00  0.00
1D.mridXsex44472001:F 0.99  0.00  0.00  0.00  0.00
1D.mridXsex46615301:F 0.74  0.00  0.00  0.00  0.23
1D.mridXsex44254401:M 0.00  0.84  0.00  0.12  0.00
1D.mridXsex44472001:M 0.00  0.86  0.00  0.00  0.00
1D.mridXsexpadilla:M  0.00  0.97  0.00  0.00  0.00
1D.mridXsex46615301:M 0.00  0.15  0.76  0.01  0.00
lg.sexF              1.00  0.00  0.00  0.00  0.00

```

```

lg.sexM          0.00  0.99 0.00 0.00 0.00
lTr.sexF         0.06  0.00 0.00 0.00 0.00
lTr.sexM         0.00  0.18 0.01 0.69 0.00

> init2$start$beta

1A.Controls46615301:F:adult:doseresponse:0.5 1A.Controls46615301:M:adult:doseresponse:0.5 1A.Controls
                                                 2.3042130          2.2208293
1A.Controls44472001:M:adult:timecourse:0.5      1A.Controlspadilla:timecourse
                                                 2.4068840          2.3791662
1A.Controls44254401:F:adult:doseresponse:1     1A.Controls44254401:M:adult:doseresponse:1 1A.Conto
                                                 2.4767856          2.4120349
1A.Controls44472001:M:adult:timecourse:2       1A.Controls44472001:F:adult:timecourse:3 1A.Conto
                                                 2.5037978          2.5263026
1A.Controls46615301:F:adult:doseresponse:4     1A.Controls46615301:M:adult:doseresponse:4 1A.Conto
                                                 2.3402287          2.2921778
1A.Controls44472001:M:adult:timecourse:4       1A.Controls44254401:F:adult:doseresponse:24 1A.Controls4
                                                 2.4870001          2.4973291
1A.Controls44254401:F:adult:doseresponse:360   1A.Controls44254401:M:adult:doseresponse:360
                                                 2.4121117          2.4076208
                                                 1D.mridXsex44472001:F
                                                 -0.7179841          -1.6884315
                                                 1D.mridXsex44472001:M
                                                 -1.2867253          -1.4256345
                                                 lg.sexF             lg.sexM
                                                 0.9327761          0.2668033
                                                 lTr.sexM
                                                 -0.1177363

> Start <- Start0 <- init2$start$beta
> tmp <- getParms("^1D", Start)
> mx <- t(sapply(strsplit(names(tmp), ":"), function(x) x[1:2]))
> mx[, 1] <- gsub("1D\\\.mridXsex", "", mx[, 1])
> tdata <- data.frame(coef = as.vector(tmp), mrid = factor(mx[, 1]), sex = factor(mx[, 2]))
> lvls <- levels(tdata$mrid)
> tdata$mrid2 <- tdata$mrid
> lvls[lvls == "44472001"] <- "44254401"
> levels(tdata$mrid2) <- lvls
> 1Dstart <- coef(lm(coef ~ 0 + sex, data = tdata))
> Start <- c(getParms("^1A", Start), 1Dstart, getParms("^lg", Start), getParms("^lTr", Start))
> tdata$res <- resid(lm(coef ~ 0 + sex, data = tdata))
> rout <- coef(lm(res ~ 0 + mrid2, data = tdata))
> Start <- list(fixed = Start, random = matrix(rout - mean(rout), nrow = length(rout), ncol = 1, dimnames = "", names(rout)), "1D"))
> if (file.exists("RatBrainrmod2.RData")) {
+   load("RatBrainrmod2.RData")
+ } else {
+   icnt <- 1
+   Maxcnt <- 50
+   repeat {
+     drmod2 <- try(nlme(cheact ~ tcmlfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, lTr = lTr), data = Controls - 1, 1D ~ sex - 1, lg ~ sex - 1, lTr ~ sex - 1), random = 1D ~ 1 | mrid2, weight = mridXsex), varPower(value = 1)), start = Start), silent = TRUE)
+     if (!inherits(drmod2, "try-error") || icnt > Maxcnt) {
+       if (icnt <= Maxcnt)

```

```

+
+           writeLines(paste("Successful in ", icnt, if (icnt > 1)
+                         "tries"
+                         else "try"))
+           else writeLines("Maxcnt exceeded")
+           break
+       }
+       icnt <- icnt + 1
+       Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+   }
+   save(drmmod2, file = "RatBraindrmod2.RData")
+ }
> drmod2

Nonlinear mixed-effects model fit by maximum likelihood
Model: cheact ~ tcfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, lTr = lTr)
Data: dta.a
Log-likelihood: -778.6022
Fixed: list(1A ~ Controls - 1, 1D ~ sex - 1, lg ~ sex - 1, lTr ~ sex - 1)
1A.Controls46615301:F:adult:doseresponse:0.5 1A.Controls46615301:M:adult:doseresponse:0.5 1A.Controls
2.3074283 2.1695385
1A.Controls44472001:M:adult:timecourse:0.5 1A.Controlspadilla:timecourse 2.3602484
2.4305050 2.3602484
1A.Controls44254401:F:adult:doseresponse:1 1A.Controls44254401:M:adult:doseresponse:1 1A.Contro
2.4824204 2.3755537
1A.Controls44472001:M:adult:timecourse:2 1A.Controls44472001:F:adult:timecourse:3 1A.Contro
2.4800487 2.5197686
1A.Controls46615301:F:adult:doseresponse:4 1A.Controls46615301:M:adult:doseresponse:4 1A.Contro
2.3363443 2.2854076
1A.Controls44472001:M:adult:timecourse:4 1A.Controls44254401:F:adult:doseresponse:24 1A.Controls4
2.4778705 2.4973292
1A.Controls44254401:F:adult:doseresponse:360 1A.Controls44254401:M:adult:doseresponse:360
2.4121119 2.4076206
1D.sexM 1g.sexF
-1.5243531 0.6202895
1Tr.sexF 1Tr.sexM
-0.4987362 -0.4493743

Random effects:
Formula: 1D ~ 1 | mrid2
          1D.(Intercept) Residual
StdDev:  2.735315e-05 8.021784

Combination of variance functions:
Structure: Different standard deviations per stratum
Formula: ~1 | mridXsex
Parameter estimates:
44254401:M 44254401:F 44472001:M 44472001:F padilla:M 46615301:M 46615301:F
1.0000000 0.7245427 0.6808252 0.8093323 0.9614803 0.7569098 0.7034310
Structure: Power of variance covariate
Formula: ~fitted()
Parameter estimates:
power
-0.8836457
Number of Observations: 615

```

Number of Groups: 3

Are the sex differences significant? If not, refit the simpler model.

```
> L <- structure(c(1, -1), names = c("1D.sexF", "1D.sexM"))
> anova(drmmod2, L = L)
```

F-test for linear combination(s)

| | 1D.sexF | 1D.sexM |
|-------|---------|----------------------|
| 1 | 1 | -1 |
| numDF | denDF | F-value p-value |
| 1 | 1 | 587 0.9724597 0.3245 |

```
> L <- structure(c(1, -1), names = c("lg.sexF", "lg.sexM"))
> anova(drmmod2, L = L)
```

F-test for linear combination(s)

| | lg.sexF | lg.sexM |
|-------|---------|--------------------|
| 1 | 1 | -1 |
| numDF | denDF | F-value p-value |
| 1 | 1 | 587 4.153118 0.042 |

```
> L <- structure(c(1, -1), names = c("lTr.sexF", "lTr.sexM"))
> anova(drmmod2, L = L)
```

F-test for linear combination(s)

| | lTr.sexF | lTr.sexM |
|-------|----------|----------------------|
| 1 | 1 | -1 |
| numDF | denDF | F-value p-value |
| 1 | 1 | 587 0.1513022 0.6974 |

The only parameter that differs between the sexes is the log power, lg.

Now test the composite hypothesis, that 1D and lTr, do not differ between the sexes:

```
> print(anova(drmmod2, L = matrix(c(1, -1, 0, 0, 0, 0, 1, -1), byrow = TRUE, nrow = 2, ncol = 4, dimnames =
+           "1D.sexM", "lTr.sexF", "lTr.sexM"))))
```

F-test for linear combination(s)

| | 1D.sexF | 1D.sexM | lTr.sexF | lTr.sexM |
|-------|---------|---------|------------------|----------|
| 1 | 1 | -1 | 0 | 0 |
| 2 | 0 | 0 | 1 | -1 |
| numDF | denDF | F-value | p-value | |
| 1 | 2 | 587 | 0.6089823 0.5442 | |

```
> Start <- drmod2$coefficients$fixed
> Start <- Start0 <- c(getParms("~1A", Start), mean(getParms("~1D", Start)), getParms("~lg", Start), me
+   Start))
> lvls <- levels(tdta$mrid)
> tdta$mrid2 <- tdta$mrid
> lvls[lvls == "44472001"] <- "44254401"
> levels(tdta$mrid2) <- lvls
> if (file.exists("RatBraindrmod3.RData")) {
+   load("RatBraindrmod3.RData")
+ } else {
+   icnt <- 1
+   Maxcnt <- 50
+   repeat {
```

```

+
+     drmod3 <- try(nlme(cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data
+                         Controls ~ 1, lD ~ 1, lg ~ sex ~ 1, lTr ~ 1), random = lD ~ 1 | mrid2, weights = varComb(
+                           mridXsex), varPower(value = 1)), start = Start), silent = TRUE)
+     if (!inherits(drmod3, "try-error") || icnt > Maxcnt) {
+       if (icnt <= Maxcnt)
+         writeLines(paste("Successful in ", icnt, if (icnt > 1)
+                           "tries"
+                           else "try"))
+       else writeLines("Maxcnt exceeded")
+       break
+     }
+     icnt <- icnt + 1
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+   }
+   save(drmod3, file = "RatBraindrmod3.RData")
+ }
> drmod3

```

Nonlinear mixed-effects model fit by maximum likelihood

```

Model: cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
Data: dta.a
Log-likelihood: -779.1021
Fixed: list(lA ~ Controls ~ 1, lD ~ 1, lg ~ sex ~ 1, lTr ~ 1)
lA.Controls46615301:F:adult:doseresponse:0.5 lA.Controls46615301:M:adult:doseresponse:0.5      lA.Controls
          2.2994567                      2.1848697
lA.Controls44472001:M:adult:timecourse:0.5           lA.Controlspadilla:timecourse
          2.4307541                      2.3595438
lA.Controls44254401:F:adult:doseresponse:1 lA.Controls44254401:M:adult:doseresponse:1      lA.C onto
          2.4817099                      2.3763071
lA.Controls44472001:M:adult:timecourse:2 lA.Controls44472001:F:adult:timecourse:3      lA.C onto
          2.4784217                      2.5206511
lA.Controls46615301:F:adult:doseresponse:4 lA.Controls46615301:M:adult:doseresponse:4      lA.C onto
          2.3362840                      2.2855062
lA.Controls44472001:M:adult:timecourse:4 lA.Controls44254401:F:adult:doseresponse:24      lA.Controls4
          2.4772606                      2.4973292
lA.Controls44254401:F:adult:doseresponse:360 lA.Controls44254401:M:adult:doseresponse:360
          2.4121119                      2.4076206
          lg.sexF                         lg.sexM
          0.6487645                      0.1793810

```

Random effects:

```

Formula: lD ~ 1 | mrid2
          lD Residual
StdDev: 1.849291e-05 8.493617

```

Combination of variance functions:

Structure: Different standard deviations per stratum

Formula: ~1 | mridXsex

Parameter estimates:

```

44254401:M 44254401:F 44472001:M 44472001:F padilla:M 46615301:M 46615301:F
1.0000000 0.7130351 0.6722112 0.8034391 0.9492855 0.7361128 0.6965392

```

Structure: Power of variance covariate

Formula: ~fitted(.)

Parameter estimates:

```

power
-0.9030996
Number of Observations: 615
Number of Groups: 3

```

Now can we collapse lg?

```

> L <- structure(c(1, -1), names = c("lg.sexF", "lg.sexM"))
> anova(drmod3, L = L)

```

```

F-test for linear combination(s)
lg.sexF lg.sexM
 1      -1
numDF denDF F-value p-value
1       1   589 43.05407 <.0001

```

No. The model in drmod3 is what we will use.

```

> Ints.a <- intervals(drmod3, which = "fixed")$fixed
> Ints90.a <- intervals(drmod3, which = "fixed", level = 0.9)$fixed
> tTab.a <- summary(drmod3)$tTable
> summary(drmod3)

```

```

Nonlinear mixed-effects model fit by maximum likelihood
Model: cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
Data: dta.a
      AIC      BIC      logLik
 1624.204 1770.118 -779.1021

```

```

Random effects:
Formula: lD ~ 1 | mrid2
           lD Residual
StdDev: 1.849291e-05 8.493617

```

Combination of variance functions:

```

Structure: Different standard deviations per stratum
Formula: ~1 | mridXsex
Parameter estimates:
44254401:M 44254401:F 44472001:M 44472001:F padilla:M 46615301:M 46615301:F
1.0000000 0.7130351 0.6722112 0.8034391 0.9492855 0.7361128 0.6965392
Structure: Power of variance covariate
Formula: ~fitted()
Parameter estimates:

```

| | power | Value | Std.Error | DF | t-value | p-value |
|--|------------|-----------|------------|-----|-----------|---------|
| lA.Controls46615301:F:adult:doseresponse:0.5 | -0.9030996 | 2.2994567 | 0.02031927 | 589 | 113.16631 | 0.0000 |
| lA.Controls46615301:M:adult:doseresponse:0.5 | | 2.1848697 | 0.02051537 | 589 | 106.49918 | 0.0000 |
| lA.Controls44472001:F:adult:timecourse:0.5 | | 2.4975689 | 0.01898572 | 589 | 131.54990 | 0.0000 |
| lA.Controls44472001:M:adult:timecourse:0.5 | | 2.4307541 | 0.01778746 | 589 | 136.65550 | 0.0000 |
| lA.Controlspadilla:timecourse | | 2.3595438 | 0.02237117 | 589 | 105.47251 | 0.0000 |
| lA.Controlspadilla:doseresponse | | 2.6150144 | 0.01508378 | 589 | 173.36603 | 0.0000 |
| lA.Controls44254401:F:adult:doseresponse:1 | | 2.4817099 | 0.01253779 | 589 | 197.93842 | 0.0000 |
| lA.Controls44254401:M:adult:doseresponse:1 | | 2.3763071 | 0.02037395 | 589 | 116.63459 | 0.0000 |

| | | | | | |
|--|--------------------|--------------------|--------------------|-----------|--------|
| 1A.Controls44472001:F:adult:timecourse:2 | 2.4948699 | 0.01672534 | 589 | 149.16710 | 0.0000 |
| 1A.Controls44472001:M:adult:timecourse:2 | 2.4784217 | 0.01349573 | 589 | 183.64494 | 0.0000 |
| 1A.Controls44472001:F:adult:timecourse:3 | 2.5206511 | 0.01410873 | 589 | 178.65894 | 0.0000 |
| 1A.Controls44472001:M:adult:timecourse:3 | 2.5146355 | 0.01150796 | 589 | 218.51279 | 0.0000 |
| 1A.Controls46615301:F:adult:doseresponse:4 | 2.3362840 | 0.01123608 | 589 | 207.92703 | 0.0000 |
| 1A.Controls46615301:M:adult:doseresponse:4 | 2.2855062 | 0.01359247 | 589 | 168.14497 | 0.0000 |
| 1A.Controls44472001:F:adult:timecourse:4 | 2.5398064 | 0.01275198 | 589 | 199.16959 | 0.0000 |
| 1A.Controls44472001:M:adult:timecourse:4 | 2.4772606 | 0.01185594 | 589 | 208.94677 | 0.0000 |
| 1A.Controls44254401:F:adult:doseresponse:24 | 2.4973292 | 0.00842870 | 589 | 296.28863 | 0.0000 |
| 1A.Controls44254401:M:adult:doseresponse:24 | 2.4824035 | 0.01231640 | 589 | 201.55273 | 0.0000 |
| 1A.Controls44254401:F:adult:doseresponse:360 | 2.4121119 | 0.00991273 | 589 | 243.33474 | 0.0000 |
| 1A.Controls44254401:M:adult:doseresponse:360 | 2.4076206 | 0.01402150 | 589 | 171.70917 | 0.0000 |
| 1D | -1.6921956 | 0.10619885 | 589 | -15.93422 | 0.0000 |
| lg.sexF | 0.6487645 | 0.10514260 | 589 | 6.17033 | 0.0000 |
| lg.sexM | 0.1793810 | 0.06931863 | 589 | 2.58777 | 0.0099 |
| 1Tr | -0.4851037 | 0.06115505 | 589 | -7.93236 | 0.0000 |
| Correlation: | | | | | |
| | 1A.C46615301:F:::0 | 1A.C46615301:M:::0 | 1A.C44472001:F:::0 | 1 | |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | 0.315 | | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | 0.000 | 0.000 | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | 0.006 | 0.005 | 0.000 | | |
| 1A.Controlspadilla:timecourse | 0.017 | 0.013 | 0.000 | | |
| 1A.Controlspadilla:doseresponse | 0.232 | 0.145 | 0.000 | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | 0.146 | 0.086 | 0.000 | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | 0.063 | 0.042 | 0.000 | | |
| 1A.Controls44472001:F:adult:timecourse:2 | -0.001 | 0.000 | 0.000 | | |
| 1A.Controls44472001:M:adult:timecourse:2 | 0.026 | 0.021 | 0.000 | | |
| 1A.Controls44472001:F:adult:timecourse:3 | 0.007 | 0.006 | 0.000 | | |
| 1A.Controls44472001:M:adult:timecourse:3 | 0.016 | 0.013 | 0.000 | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | 0.021 | 0.013 | 0.000 | | |
| 1A.Controls46615301:M:adult:doseresponse:4 | 0.012 | 0.008 | 0.000 | | |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.005 | 0.004 | 0.000 | | |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.007 | 0.006 | 0.000 | | |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | | |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 | | |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | | |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 | | |
| 1D | -0.716 | -0.441 | 0.000 | | |
| lg.sexF | -0.516 | -0.337 | 0.001 | | |
| lg.sexM | -0.626 | -0.382 | 0.000 | | |
| 1Tr | 0.056 | 0.047 | -0.001 | | |
| | 1A.C44254401:F:::1 | 1A.C44254401:M:::1 | 1A.C44472001:F:::2 | 1 | |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | | | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | | | |
| 1A.Controlspadilla:timecourse | | | | | |
| 1A.Controlspadilla:doseresponse | | | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | 0.028 | | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | 0.055 | 0.035 | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | 0.036 | 0.054 | 0.094 | | |
| 1A.Controls44472001:F:adult:timecourse:3 | 0.040 | 0.031 | 0.098 | | |
| 1A.Controls44472001:M:adult:timecourse:3 | 0.026 | 0.034 | 0.069 | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | 0.010 | 0.007 | 0.012 | | |

| | | | |
|--|--------------------|--------------------|----------------------|
| 1A.Controls46615301:M:adult:doseresponse:4 | 0.006 | 0.005 | 0.010 |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.021 | 0.017 | 0.052 |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.012 | 0.014 | 0.032 |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1D | -0.197 | -0.092 | -0.003 |
| lg.sexF | -0.093 | -0.109 | -0.037 |
| lg.sexM | -0.190 | -0.039 | -0.057 |
| 1Tr | 0.115 | 0.117 | 0.320 |
| | 1A.C44472001:M:::3 | 1A.C46615301:F:::4 | 1A.C46615301:M:::4 1 |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | |
| 1A.Controlspadilla:timecourse | | | |
| 1A.Controlspadilla:doseresponse | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | | | |
| 1A.Controls44472001:F:adult:timecourse:3 | | | |
| 1A.Controls44472001:M:adult:timecourse:3 | | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | 0.009 | | |
| 1A.Controls46615301:M:adult:doseresponse:4 | 0.007 | 0.002 | |
| 1A.Controls44472001:F:adult:timecourse:4 | 0.033 | 0.006 | 0.005 |
| 1A.Controls44472001:M:adult:timecourse:4 | 0.023 | 0.004 | 0.003 |
| 1A.Controls44254401:F:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1D | -0.031 | -0.031 | -0.018 |
| lg.sexF | -0.100 | -0.035 | -0.024 |
| lg.sexM | -0.039 | -0.033 | -0.021 |
| 1Tr | 0.217 | 0.039 | 0.032 |
| | 1A.C44254401:F:::2 | 1A.C44254401:M:::2 | 1A.C44254401:F:::3 1 |
| 1A.Controls46615301:M:adult:doseresponse:0.5 | | | |
| 1A.Controls44472001:F:adult:timecourse:0.5 | | | |
| 1A.Controls44472001:M:adult:timecourse:0.5 | | | |
| 1A.Controlspadilla:timecourse | | | |
| 1A.Controlspadilla:doseresponse | | | |
| 1A.Controls44254401:F:adult:doseresponse:1 | | | |
| 1A.Controls44254401:M:adult:doseresponse:1 | | | |
| 1A.Controls44472001:F:adult:timecourse:2 | | | |
| 1A.Controls44472001:M:adult:timecourse:2 | | | |
| 1A.Controls44472001:F:adult:timecourse:3 | | | |
| 1A.Controls44472001:M:adult:timecourse:3 | | | |
| 1A.Controls46615301:F:adult:doseresponse:4 | | | |
| 1A.Controls46615301:M:adult:doseresponse:4 | | | |
| 1A.Controls44472001:F:adult:timecourse:4 | | | |
| 1A.Controls44472001:M:adult:timecourse:4 | | | |
| 1A.Controls44254401:F:adult:doseresponse:24 | | | |
| 1A.Controls44254401:M:adult:doseresponse:24 | 0.000 | | |
| 1A.Controls44254401:F:adult:doseresponse:360 | 0.000 | 0.000 | |

| | | | |
|--|-------|-------|-------|
| 1A.Controls44254401:M:adult:doseresponse:360 | 0.000 | 0.000 | 0.000 |
| 1D | 0.000 | 0.000 | 0.000 |
| lg.sexF | 0.000 | 0.000 | 0.000 |
| lg.sexM | 0.000 | 0.000 | 0.000 |
| 1Tr | 0.000 | 0.000 | 0.000 |

Standardized Within-Group Residuals:

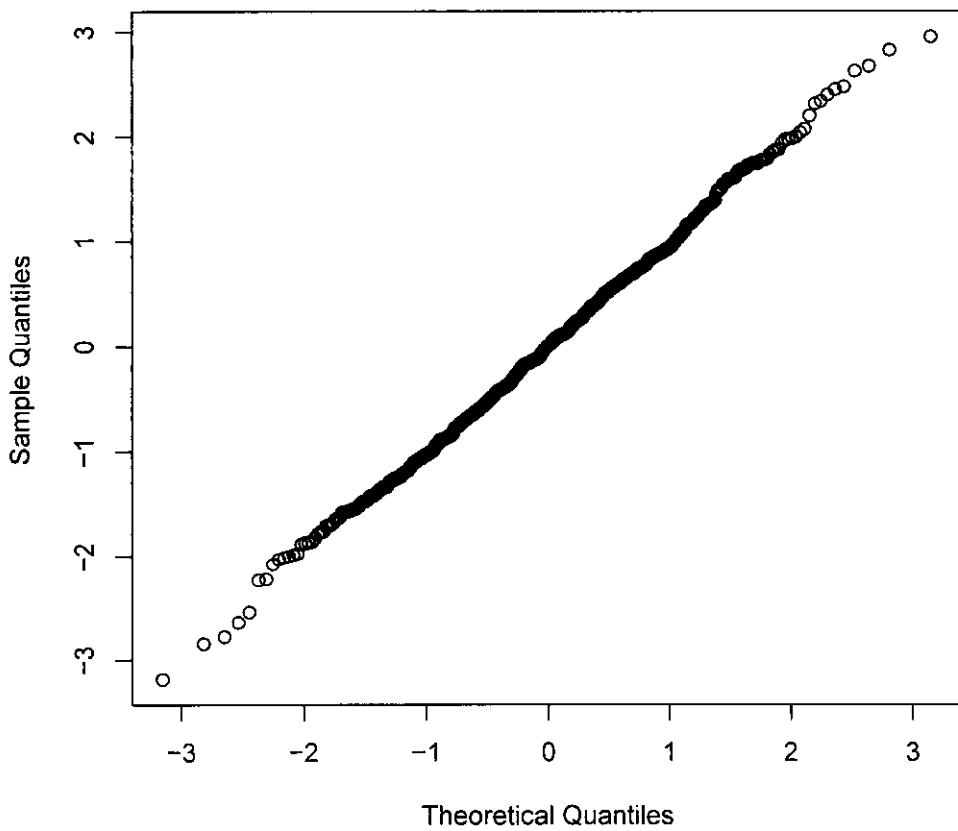
| Min | Q1 | Med | Q3 | Max |
|-------------|--------------|--------------|-------------|-------------|
| -3.19056227 | -0.702304054 | -0.002623486 | 0.668629202 | 2.951635776 |

Number of Observations: 615

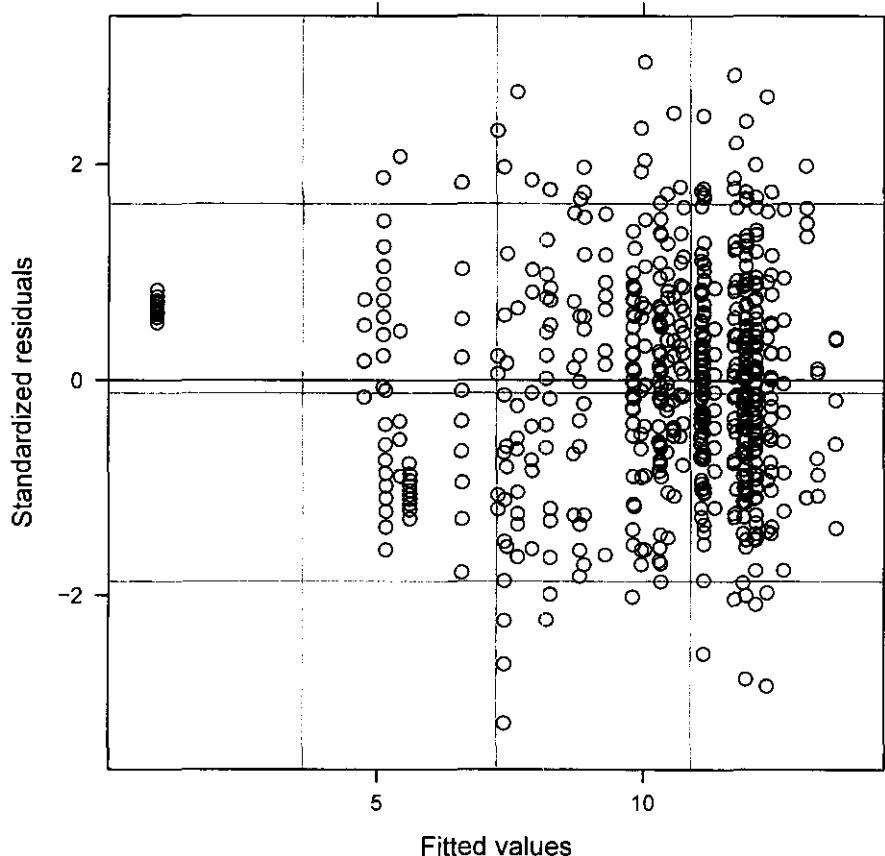
Number of Groups: 3

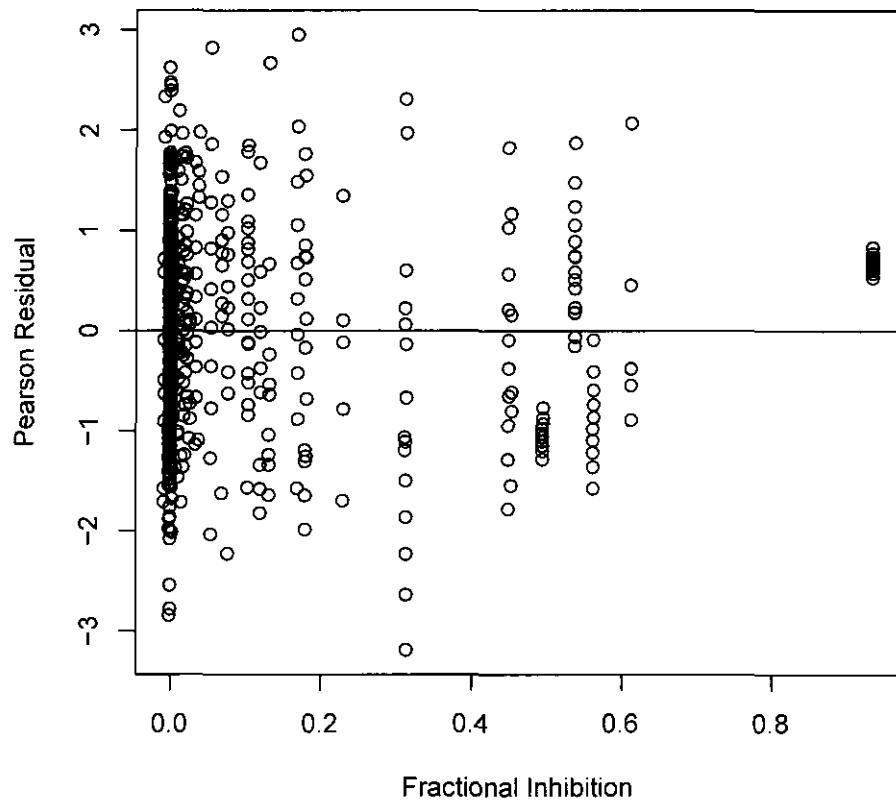
Diagnostic plots for this model.

QQ Plot of (Pearson) Scaled Residuals

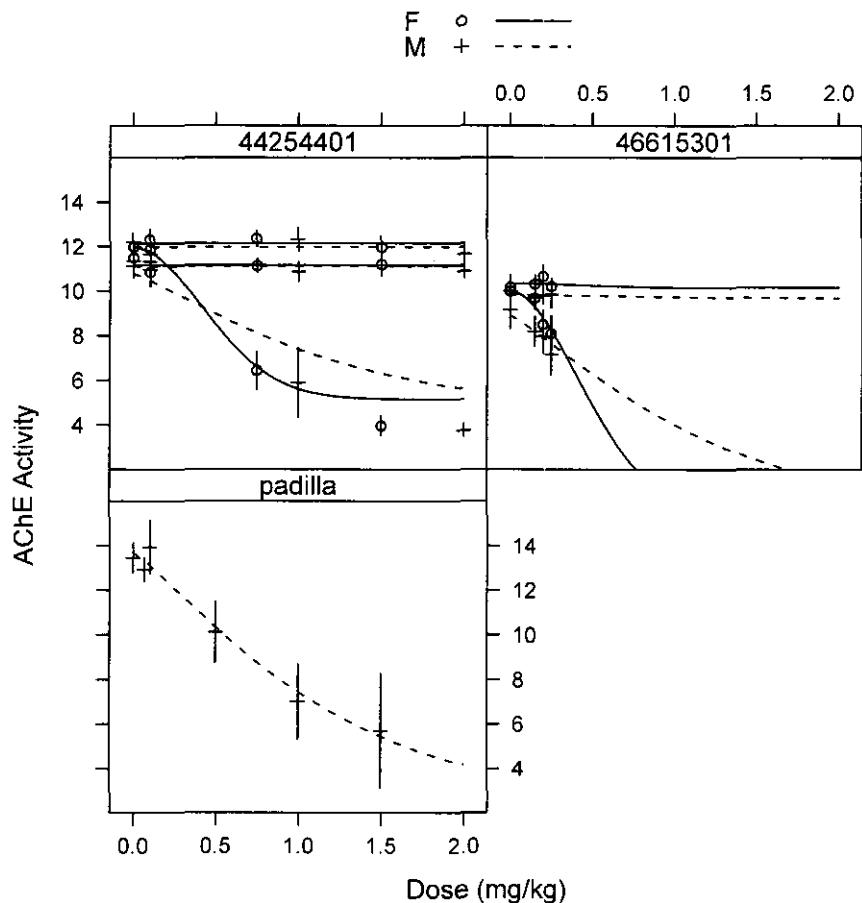
Normal Q-Q Plot

Scaled Residuals versus Fitted Activity Level

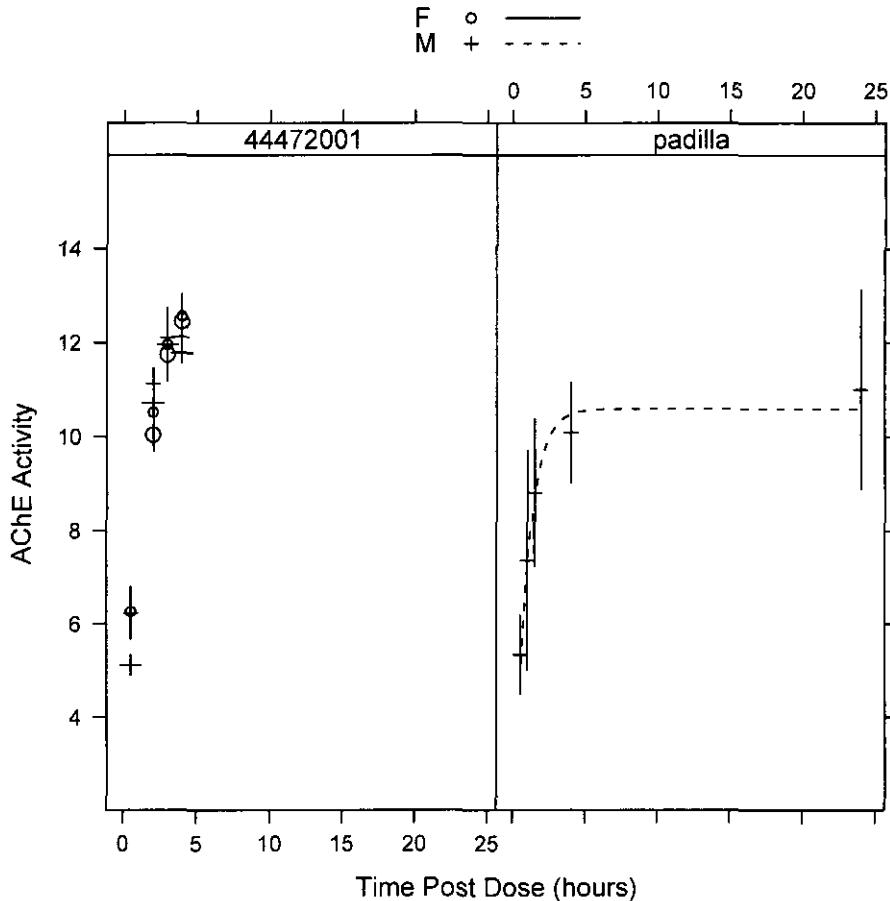




Next, dose-response and recovery curves with means and 95% confidence intervals from the data.



Timecourses:



In the time course plot for 44472001, the larger symbols correspond to the fitted value for that sex and time point from the model.

4 Analysis of PND11 to Adult Potency Ratios in MRID 46615301

This MRID contain both PND11 and adult dose response information and pnd11 time-course information that can be used to evaluate the ratio of potencies between adults and juveniles.

Extract the data for this subanalysis, and summarize the design used:

```
> dta.ajr <- CleanUp(subset(dta, mrid == "46615301"))
> with(dta.ajr, print(table(dose, tmpstds, age), zero.print = "."))
, , age = adult

      tmpstds
dose   0.5 1 1.5 2 3 4 6
  0     20 . . . . 17 .
  0.075 . . . . . . .
  0.1   . . . . . . .
  0.125 . . . . . . .
  0.15  20 . . . . 20 .
  0.2   20 . . . . 20 .
```

```

0.25 20 . . . . 20 .

, , age = pnd11

tmpstds
dose 0.5 1 1.5 2 3 4 6
0 20 10 . 10 . 10 .
0.075 20 . . . .
0.1 29 10 10 9 10 10 10
0.125 20 . . . . .
0.15 20 . . . . .
0.2 . . . . .
0.25 . . . .

```

Two features stand out here: there is no time course component in the adult dataset (the analysis of the adult data, above, shows that AChE activity has pretty much returned to normal by four hours, so that time point is useless for estimating recovery half life), and there are no controls for three of the seven pnd11 time points. Furthermore, the analysis of the pnd11 control groups reported above shows that they are heterogeneous, with no pattern.

The dose-response component of both age groups was carried out at 0.5 hours after dosing. That value will be the "delta" in the dose-time response model. If we drop the four hour data in the adults, we only need a half-life parameter in the pnd11 animals, as the dose-response data, at 0.5 hour, will be time "0" in the model. Dropping this time group allows us to simultaneously estimate the dose-response and timecourse parameters, simplifying the analysis. There is minimal disadvantage, since AChE activity has substantially recovered by four hours.

```
> dta.ajr <- CleanUp(subset(dta.ajr, (age == "pnd11") | (age == "adult" & tmpstds == 0.5)))
```

Since there is only a single mrid, there are no random effects to consider. We will use generalized non-linear least squares to fit the model, allowing for a power variance model. In addition, given the relatively low levels of inhibition seen in this study, we will not try to estimate the horizontal asymptote parameterized by tz.

Get initial values:

```

> formals(tcmfn4)$delta <- min(dta.ajr$tmpstds[dta.ajr$tmpstds > 0])
> formals(tcmfn4)$tz <- -10
> initfile <- paste("initvals-brain-DR-4.RData", sep = "")
> if (!file.exists(initfile)) {
+   lA.start <- lm(I(log(cheact)) ~ Controls - 1, data = CleanUp(subset(dta.ajr, dose %in% 0)))
+   lA.start <- coef(lA.start)[paste("Controls", levels(dta.ajr$Controls), sep = "")]
+   names(lA.start) <- levels(dta.ajr$Controls)
+   mn <- mean(lA.start, na.rm = TRUE)
+   lA.start[is.na(lA.start)] <- mn
+   Start <- with(dta.ajr, c(lA.start, rep(-0.72, nlevels(sex:age)), rep(0, nlevels(sex:age)), rep(1,
+     init4 <- GetInitialValues(cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), d
+       Controls - 1, lD ~ age:sex - 1, lg ~ age:sex - 1, lTr ~ sex - 1), start = Start, weights = va
+       save(init4, file = initfile)
+   } else load(initfile)
> tmp <- t(init4$Redundancy[[1]]$Eigens)
> round(tmp[, 1:6], digits = 2)

```

| | [,1] | [,2] | [,3] | [,4] | [,5] | [,6] |
|--|-------|------|------|------|------|------|
| CondIndex | 10.82 | 7.97 | 6.67 | 6.28 | 4.64 | 4.47 |
| mu | 0.16 | 0.21 | 0.25 | 0.27 | 0.36 | 0.38 |
| lA.Controls46615301:F:adult:doseresponse:0.5 | 0.00 | 0.00 | 0.00 | 0.67 | 0.00 | 0.00 |
| lA.Controls46615301:M:adult:doseresponse:0.5 | 0.00 | 0.00 | 0.55 | 0.00 | 0.00 | 0.00 |
| lA.Controls46615301:F:pnd11:doseresponse:0.5 | 0.00 | 0.54 | 0.00 | 0.00 | 0.00 | 0.00 |

| | | | | | | |
|--|------|------|------|------|------|------|
| 1A.Controls46615301:M:pnd11:doseresponse:0.5 | 0.26 | 0.00 | 0.00 | 0.00 | 0.04 | 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:1 | 0.00 | 0.03 | 0.00 | 0.00 | 0.00 | 0.08 |
| 1A.Controls46615301:M:pnd11:timecourse:1 | 0.02 | 0.00 | 0.00 | 0.00 | 0.04 | 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:1.5 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.45 |
| 1A.Controls46615301:M:pnd11:timecourse:1.5 | 0.01 | 0.00 | 0.00 | 0.00 | 0.34 | 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:2 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.39 |
| 1A.Controls46615301:M:pnd11:timecourse:2 | 0.00 | 0.00 | 0.00 | 0.00 | 0.25 | 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:3 | 0.00 | 0.03 | 0.00 | 0.00 | 0.00 | 0.61 |
| 1A.Controls46615301:M:pnd11:timecourse:3 | 0.01 | 0.00 | 0.00 | 0.00 | 0.63 | 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:4 | 0.00 | 0.02 | 0.00 | 0.00 | 0.00 | 0.32 |
| 1A.Controls46615301:M:pnd11:timecourse:4 | 0.01 | 0.00 | 0.00 | 0.00 | 0.37 | 0.00 |
| 1A.Controls46615301:F:pnd11:timecourse:6 | 0.00 | 0.03 | 0.00 | 0.00 | 0.00 | 0.28 |
| 1A.Controls46615301:M:pnd11:timecourse:6 | 0.01 | 0.00 | 0.00 | 0.00 | 0.37 | 0.00 |
| 1D.ageadult:sexF | 0.00 | 0.00 | 0.00 | 0.98 | 0.00 | 0.00 |
| 1D.agepnd11:sexF | 0.00 | 0.98 | 0.00 | 0.00 | 0.00 | 0.01 |
| 1D.ageadult:sexM | 0.00 | 0.00 | 0.98 | 0.00 | 0.00 | 0.00 |
| 1D.agepnd11:sexM | 0.98 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| lg.ageadult:sexF | 0.00 | 0.00 | 0.00 | 0.80 | 0.00 | 0.00 |
| lg.agepnd11:sexF | 0.00 | 0.79 | 0.00 | 0.00 | 0.00 | 0.02 |
| lg.ageadult:sexM | 0.00 | 0.00 | 0.82 | 0.00 | 0.00 | 0.00 |
| lg.agepnd11:sexM | 0.92 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 |
| 1Tr.sexF | 0.00 | 0.16 | 0.00 | 0.00 | 0.00 | 0.78 |
| 1Tr.sexM | 0.08 | 0.00 | 0.00 | 0.86 | 0.00 | 0.00 |

Estimates of lg and ID are possibly confounded, but the maximum condition index is probably small enough to go ahead and try a fit. Now, the fit for the control option coded in 'Control2':

```
> Start <- init4$start$beta
> dta.ajr$A.S <- with(dta.ajr, interaction(age, sex, drop = TRUE, sep = ":"))
> drmod4 <- try(gnls(cheact ~ tcmlfn4(dose, tmpstds, 1A = 1A, 1D = 1D, lg = lg, lTr = lTr), data = dta.a
+   Controls - 1, 1D ~ age:sex - 1, lg ~ age:sex - 1, lTr ~ sex - 1), start = Start, weights = varCom
+   A.S), varPower(value = 1)))
```

Look for simplifications: try to collapse ID, lg, and lTr across sex:

```
> anova(drmod4, L = matrix(c(1, -1, 0, 0, 0, -1, 1), nrow = 2, ncol = 4, byrow = TRUE, dimnames = li
+   "1D.ageadult:sexM", "1D.agepnd11:sexF", "1D.agepnd11:sexM")))
```

Denom. DF: 252

F-test for linear combination(s)

| | 1D.ageadult:sexF | 1D.agepnd11:sexF | 1D.ageadult:sexM | 1D.agepnd11:sexM |
|-------|------------------|------------------|------------------|------------------|
| 1 | 1 | 0 | -1 | 0 |
| 2 | 0 | -1 | 0 | 1 |
| numDF | F-value | p-value | | |
| 1 | 2 | 0.3216101 | 0.7253 | |

```
> anova(drmod4, L = matrix(c(1, -1, 0, 0, 0, -1, 1), nrow = 2, ncol = 4, byrow = TRUE, dimnames = li
+   "lg.ageadult:sexM", "lg.agepnd11:sexF", "lg.agepnd11:sexM")))
```

Denom. DF: 252

F-test for linear combination(s)

| | lg.ageadult:sexF | lg.agepnd11:sexF | lg.ageadult:sexM | lg.agepnd11:sexM |
|-------|------------------|------------------|------------------|------------------|
| 1 | 1 | 0 | -1 | 0 |
| 2 | 0 | -1 | 0 | 1 |
| numDF | F-value | p-value | | |
| 1 | 2 | 0.3352771 | 0.7155 | |

```
> anova(drmmod4, L = c(lTr.sexF = 1, lTr.sexM = -1))
```

```

Denom. DF: 252
F-test for linear combination(s)
lTr.sexF lTr.sexM
      1       -1
numDF   F-value p-value
1       1 0.2174187  0.6414

```

None of the effects differs between sexes. What is the joint significance of collapsing the remaining effects across sex, simultaneously?

```

Denom. DF: 252
F-test for linear combination(s)
  1D.ageadult:sexF 1D.agepnd11:sexF 1D.ageadult:sexM 1D.agepnd11:sexM lg.ageadult:sexF lg.agepnd11:sexF
1             1                 0              -1                 0                 0                 0
2             0                 1               0                -1                 0                 0
3             0                 0               0                 0                -1                 0
4             0                 0               0                 0                 0                 0
5             0                 0               0                 0                 0                 0
  lTr.sexM
1             0
2             0
3             0
4             0
5             1
  numDF   F-value p-value
1      5 0.2234987 0.9522

```

Now fit the simplified model:

```

> ParmS <- coef(drmod4)
> Start <- c(getParms("lA", ParmS), mean(getParms("lD.ageadult", ParmS)), mean(getParms("lD.agepnd11",
+   ParmS)), mean(getParms("lg.agepnd11", ParmS)), mean(getParms("lTr", ParmS)))
> drmod5 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr), data = dta.a,
+   factor(Controls) - 1, lD ~ age - 1, lg ~ age - 1, lTr ~ 1), start = Start, weights = varComb(varL
+   A.S), varPower(value = 1)))

```

Finally, compare the reduced to the fuller parameterization; look at AIC and BIC, as well as the P-value for the overall comparison. Now, try the alternative control parameterization:

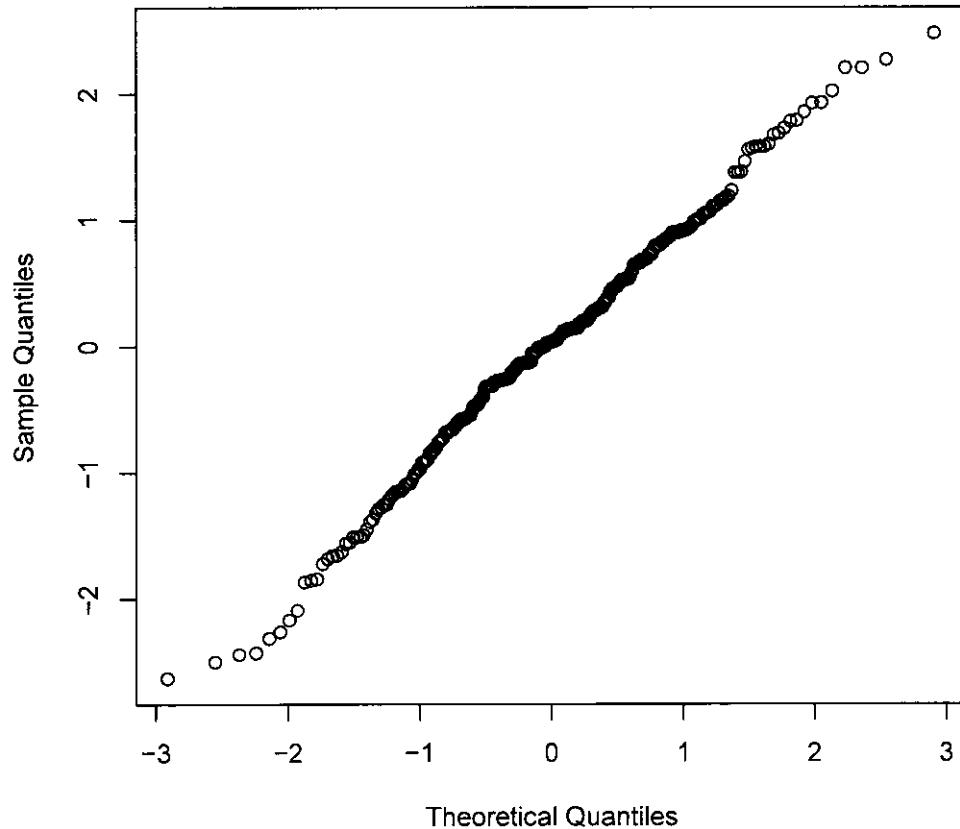
```
> anova(drmmod4, drmod5)
```

| | Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|--|--------|----|-----|----------|----------|-----------|---------|-----------------|
| | drmod4 | 1 | 31 | 637.1712 | 749.6274 | -287.5856 | | |
| | drmod5 | 2 | 26 | 628.4058 | 722.7239 | -288.2029 | 1 vs 2 | 1.234607 0.9415 |

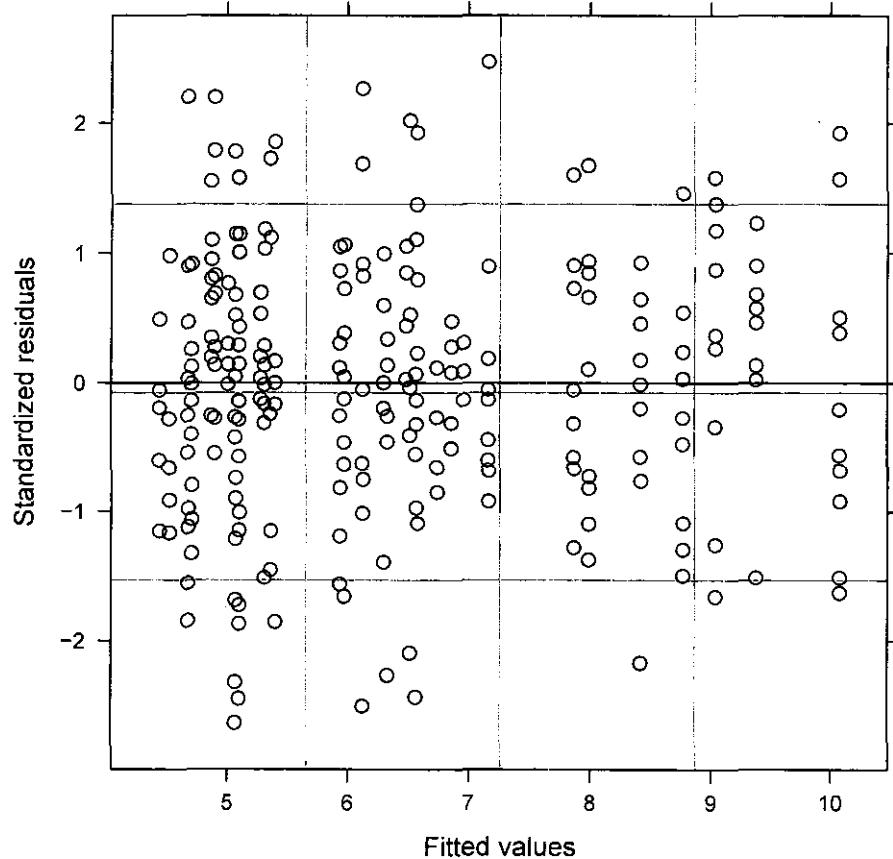
Note that the P-value is similar to that for the total contrast. The AIC and BIC for the simpler model is smaller. Diagnostic plots for this fit:

QQ Plot of (Pearson) Scaled Residuals:

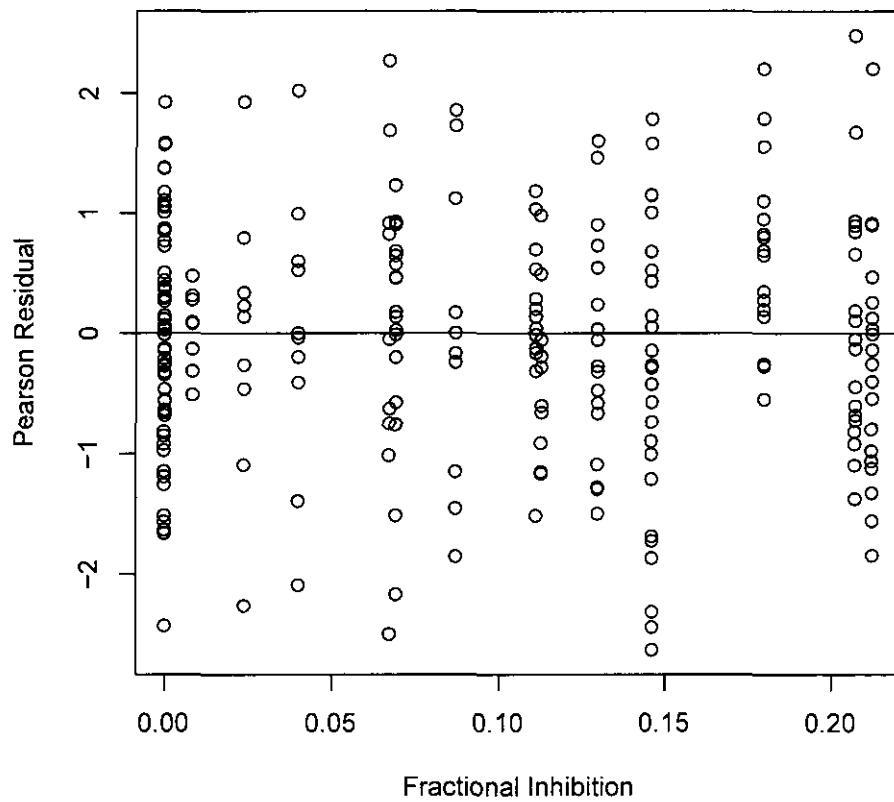
Normal Q-Q Plot



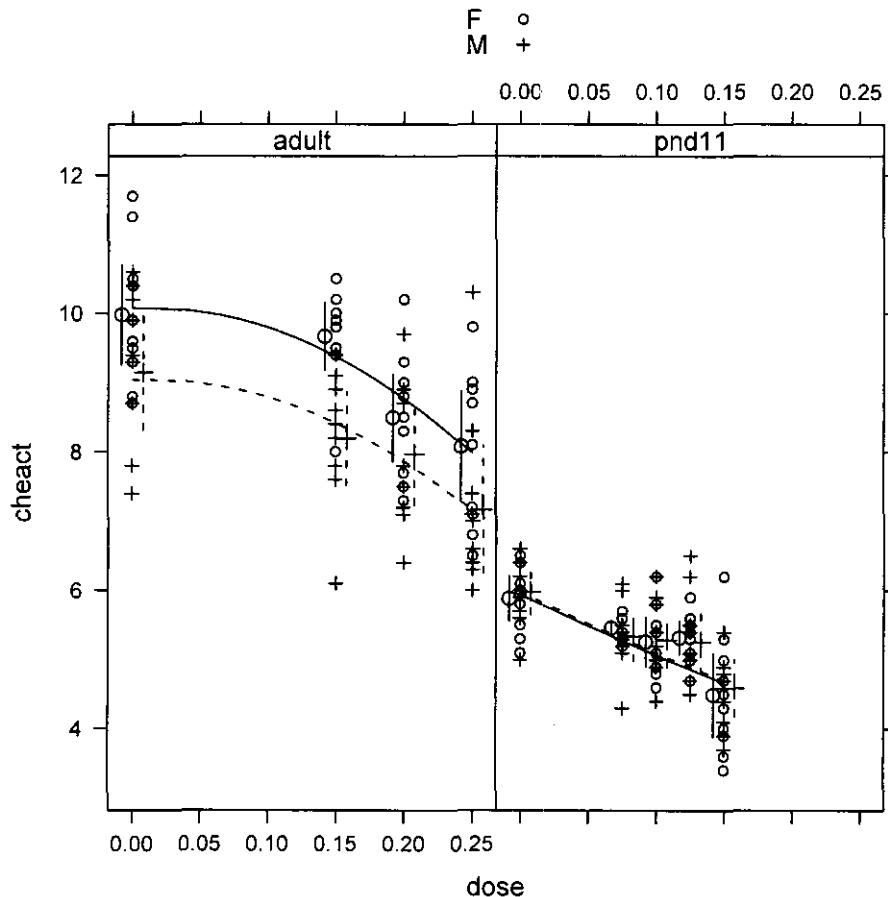
Scaled residuals versus fitted values:



Scaled Residuals versus Predicted Fraction of Inhibition:

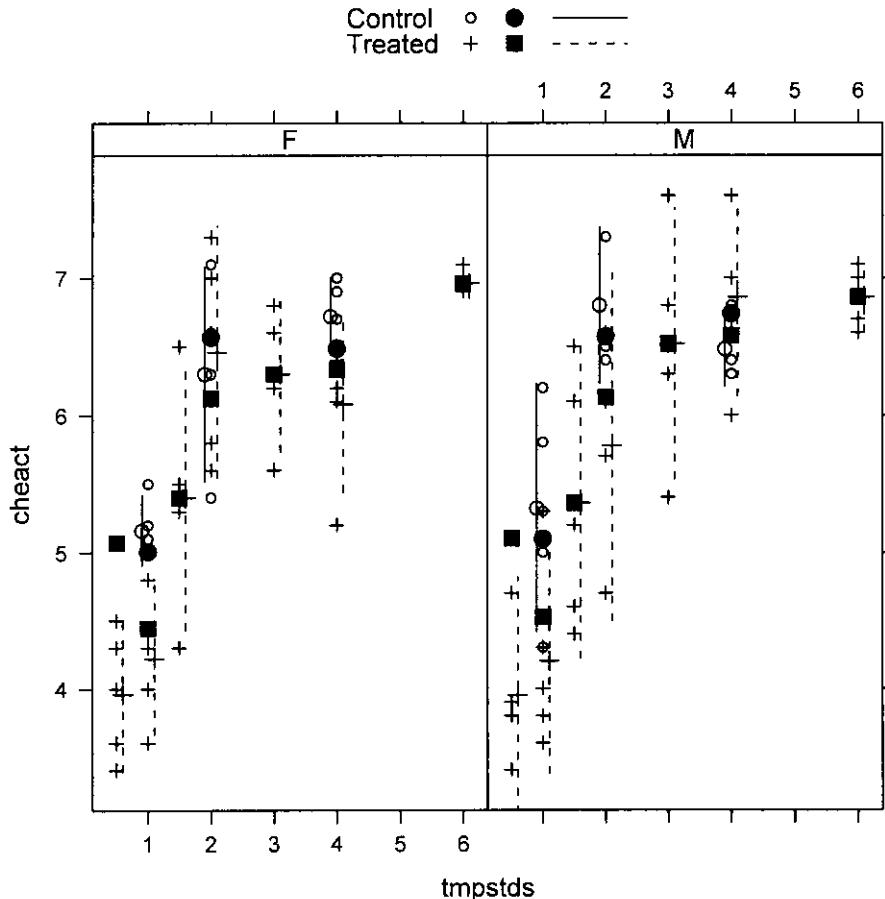


Dose-Response Curves, by age:



Here, the dose-group means for males and females are displaced slightly to the right and left, respectively, of their correct place to make it easier to distinguish the means from the raw data points.

Time Course for pnd11 Animals



Larger, solid symbols represent fitted values from the model. Confidence intervals are 95% confidence intervals for the means.

Two values of interest from this model are the ratio of the adult to the pnd11 BMDs, and the pnd11 recovery half-life. The ratio is conveniently calculated by exponentiating the difference between the log BMDs (ID) for each age group. Confidence intervals are calculated by calculating the standard error for the linear contrast of the two log BMDs, and exponentiating the approximate normal-theory confidence interval for the difference of the log BMDs. This is all carried out by the code below:

```

> cov <- drmod5$varBeta
> Cn <- coef(drmod5)
> Cn[] <- 0
> Cn["1D.ageadult"] <- 1
> Cn["1D.agepnd11"] <- -1
> lpotrat <- Cn %*% coef(drmod5)
> selpotrat <- sqrt(Cn %*% cov %*% Cn)
> potrat <- exp(lpotrat)
> CIpotrat <- exp(lpotrat + qnorm(c(0.025, 0.975)) * selpotrat)

> tTab.j <- summary(drmod5)$tTable
> Ints.j <- intervals(drmod5, which = "coef")$coef
> Ints90.j <- intervals(drmod5, which = "coef", level = 0.9)$coef
> summary(drmod5)

```

Generalized nonlinear least squares fit
 Model: cheact ~ tcmlfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
 Data: dta.ajr
 AIC BIC logLik
 628.4058 722.7239 -288.2029

Combination of variance functions:
 Structure: Different standard deviations per stratum
 Formula: ~1 + A.S
 Parameter estimates:
 pnd11:M pnd11:F adult:M adult:F
 1.0000000 0.9053743 2.6192931 2.5166221
 Structure: Power of variance covariate
 Formula: ~fitted()
 Parameter estimates:
 power
 -1.073175

Coefficients:

| | | Value | Std.Error | t-value | p-value |
|--|--|------------|-----------|-----------|---------|
| lA.factor(Controls)46615301:F:adult:doseresponse:0.5 | | 2.3102509 | 0.0230920 | 100.04541 | 0.0000 |
| lA.factor(Controls)46615301:M:adult:doseresponse:0.5 | | 2.2016830 | 0.0267535 | 82.29512 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | 1.7813223 | 0.0232949 | 76.46849 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | 1.7874783 | 0.0243113 | 73.52463 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:1 | | 1.6109279 | 0.0459830 | 35.03310 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:1 | | 1.6289244 | 0.0488413 | 33.35136 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:1.5 | | 1.7775526 | 0.0552622 | 32.16582 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:1.5 | | 1.7701176 | 0.0606330 | 29.19397 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:2 | | 1.8822172 | 0.0274877 | 68.47493 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:2 | | 1.8828072 | 0.0304055 | 61.92330 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:3 | | 1.8814587 | 0.0448206 | 41.97756 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:3 | | 1.9157835 | 0.0456381 | 41.97771 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:4 | | 1.8697539 | 0.0265684 | 70.37520 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:4 | | 1.9080930 | 0.0270174 | 70.62462 | 0.0000 |
| lA.factor(Controls)46615301:F:pnd11:timecourse:6 | | 1.9487004 | 0.0315931 | 61.68113 | 0.0000 |
| lA.factor(Controls)46615301:M:pnd11:timecourse:6 | | 1.9342284 | 0.0353103 | 54.77809 | 0.0000 |
| lD.ageadult | | -1.7302380 | 0.1215729 | -14.23210 | 0.0000 |
| lD.agepnd11 | | -2.7012272 | 0.2708515 | -9.97309 | 0.0000 |
| lg.ageadult | | 0.8326861 | 0.3299197 | 2.52391 | 0.0122 |
| lg.agepnd11 | | 0.0169948 | 0.3657326 | 0.04647 | 0.9630 |
| lTr | | 0.2921068 | 0.5279525 | 0.55328 | 0.5806 |

Correlation:

| | lA.(C)46615301:F:: | lA.(C)46615301:M:: | lA.(C)46615301:M:pnd11:timecourse:1 | lA.(C)46615301:M:pnd11:timecourse:2 | lA.(C)46615301:M:pnd11:timecourse:3 |
|--|--------------------|--------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| lA.factor(Controls)46615301:M:adult:doseresponse:0.5 | 0.441 | | | | |
| lA.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | 0.000 | | | | |
| lA.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | 0.000 | | | | |
| lA.factor(Controls)46615301:F:pnd11:timecourse:1 | 0.000 | | | | |
| lA.factor(Controls)46615301:M:pnd11:timecourse:1 | 0.000 | | | | |
| lA.factor(Controls)46615301:F:pnd11:timecourse:1.5 | 0.000 | | | | |
| lA.factor(Controls)46615301:M:pnd11:timecourse:1.5 | 0.000 | | | | |
| lA.factor(Controls)46615301:F:pnd11:timecourse:2 | 0.000 | | | | |
| lA.factor(Controls)46615301:M:pnd11:timecourse:2 | 0.000 | | | | |
| lA.factor(Controls)46615301:F:pnd11:timecourse:3 | 0.000 | | | | |
| | | | | | -0.048 |

| | | | |
|--|-------------------------|--------|--------|
| 1A.factor(Controls)46615301:M:pnd11:timecourse:3 | 0.000 | 0.000 | -0.047 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | 0.000 | 0.000 | -0.050 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | 0.000 | 0.000 | -0.049 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:6 | 0.000 | 0.000 | -0.066 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:6 | 0.000 | 0.000 | -0.059 |
| 1D.ageadult | -0.681 | -0.588 | 0.000 |
| 1D.agepnd11 | 0.000 | 0.000 | -0.577 |
| lg.ageadult | -0.434 | -0.375 | 0.000 |
| lg.agepnd11 | 0.000 | 0.000 | -0.285 |
| 1Tr | 0.000 | 0.000 | -0.233 |
| 1A.f(C)46615301:F:11::1 | 1A.f(C)46615301:M:11::1 | 1A. | |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | 0.029 | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1.5 | 0.072 | 0.068 | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1.5 | 0.066 | 0.062 | 0 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | 0.061 | 0.057 | 0 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | 0.048 | 0.045 | 0 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:3 | 0.074 | 0.070 | 0 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:3 | 0.073 | 0.068 | 0 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | 0.046 | 0.043 | 0 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | 0.045 | 0.042 | 0 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:6 | 0.042 | 0.039 | 0 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:6 | 0.037 | 0.035 | 0 |
| 1D.ageadult | 0.000 | 0.000 | 0 |
| 1D.agepnd11 | -0.100 | -0.094 | -0 |
| lg.ageadult | 0.000 | 0.000 | 0 |
| lg.agepnd11 | -0.063 | -0.059 | -0 |
| 1Tr | 0.092 | 0.086 | 0 |
| 1A.(C)46615301:F:11::2 | 1A.(C)46615301:M:11::2 | 1A.(C) | |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | 0.150 | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:3 | 0.261 | 0.206 | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:3 | 0.256 | 0.203 | 0.3 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | 0.171 | 0.135 | 0.2 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | 0.168 | 0.133 | 0.2 |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:6 | 0.166 | 0.131 | 0.2 |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:6 | 0.148 | 0.117 | 0.2 |
| 1D.ageadult | 0.000 | 0.000 | 0.0 |
| 1D.agepnd11 | -0.017 | -0.014 | 0.0 |
| lg.ageadult | 0.000 | 0.000 | 0.0 |
| lg.agepnd11 | -0.011 | -0.009 | 0.0 |
| 1Tr | 0.405 | 0.321 | 0.5 |
| 1A.(C)46615301:F:11::4 | 1A.(C)46615301:M:11::4 | 1A.(C) | |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | | | |

| | | | |
|--|--------|--------|--------|
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:3 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:3 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | 0.159 | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:6 | 0.159 | 0.156 | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:6 | 0.142 | 0.140 | |
| 1D.ageadult | 0.000 | 0.000 | 0.1 |
| 1D.agepnd11 | 0.063 | 0.062 | 0.0 |
| lg.ageadult | 0.000 | 0.000 | 0.0 |
| lg.agepnd11 | 0.040 | 0.039 | 0.0 |
| 1Tr | 0.397 | 0.390 | 0.3 |
| | 1D.g11 | lg.gdl | lg.g11 |
| 1A.factor(Controls)46615301:M:adult:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:doseresponse:0.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:1.5 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:1.5 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:2 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:3 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:3 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:4 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:4 | | | |
| 1A.factor(Controls)46615301:F:pnd11:timecourse:6 | | | |
| 1A.factor(Controls)46615301:M:pnd11:timecourse:6 | | | |
| 1D.ageadult | 0.000 | | |
| 1D.agepnd11 | 0.872 | 0.000 | |
| lg.ageadult | 0.292 | 0.000 | 0.183 |
| lg.agepnd11 | | | |
| 1Tr | | | |

Standardized residuals:

| Min | Q1 | Med | Q3 | Max |
|-------------|-------------|------------|------------|------------|
| -2.63161129 | -0.57615458 | 0.02978201 | 0.65794482 | 2.47533045 |

Residual standard error: 4.000876

Degrees of freedom: 278 total; 257 residual

5 Summary

The critical estimates from this analysis are listed below. They are printed with greater than usual precision, in case they are to be used in further computation. For reporting, round to two or three significant digits. BMD has units mg/kg, and times are in hours.

species RAT

mrid [1] "44254401" "44472001" "padilla" "46615301"

Adult 1D (standard error) -1.69219560519953 (0.106198845210994)

Adult BMD (95% CI) 0.184114836396363 (0.150069033707590, 0.225884528898284)

Adult BMDL, the one-sided lower 95% CL 0.155096996177245

Results from the comparative ChE study (MRID 46615301)

PND 11 1D (standard error) -2.70122721948004 (0.27085153406102)

PND11 BMD (95% CI) 0.0671230874126777 (0.0393760224076288, 0.114422650850002)

PND11 BMDL, the one-sided lower 95% CL 0.0429228876765208

Adult 1D (standard error) -1.73023796708349 (0.121572927884797)

Adult BMD (95% CI) 0.177242227135152 (0.139506520733877, 0.225185223705461)

Adult BMDL, the one-sided lower 95% CL 0.145013117791285

Ratio of Adult to PND11 BMD (95% CI) 2.64055534343129 (1.4756608386466, 4.72502375824948)

Adult lTr (standard error) :

| Value | Std.Error |
|-------------|------------|
| -0.48510375 | 0.06115505 |

Adult Recovery Half-life (95% CI) :

| lower | est. | upper |
|-----------|-----------|-----------|
| 0.5472523 | 0.6156333 | 0.6925588 |

PND11 Recovery Half-Life (95% CI) 1.33924602878689 (0.473521959557482, 3.78774392490183)

Save everything:

```
> save.image(file = "RatBrainDR.RData")
```

Save the results for incorporating into a database:

```
> oxamyl.oral.brain <- list(mrid = levels(dta$mrid), species = "RAT", BMDs = list(adult = list(combined
+   "Value"], 1D.se = tTab.a["1D", "Std.Error"], BMD = exp(Ints.a["1D", "est."]), BMD.CI = exp(Ints.a
+   "upper"))], BMDL = exp(Ints90.a["1D", "lower"])), pnd11 = list(combined = list(1D = tTab.j["1D.a
+   1D.se = tTab.j["1D.agepnd11", "Std.Error"], BMD = exp(Ints.j["1D.agepnd11", "est."]), BMD.CI = ex
+   c("lower", "upper"))], BMDL = exp(Ints90.j["1D.agepnd11", "lower"]))), HalfLives = list(adul
+   rownames(tTab.a)), "Value"], 1Tr.se = tTab.a[grep("^1Tr", rownames(tTab.a)), "Std.Error"], Tr = e
+   rownames(Ints.a)), "est."]), Tr.CI = exp(Ints.a[c("lower", "upper"))]), pnd11 = list(lTr = tTab.j
+   lTr.se = tTab.j["lTr", "Std.Error"], Tr = exp(Ints.j["lTr", "est."]), Tr.CI = exp(Ints.j["lTr", c
> save(oxamyl.oral.brain, file = file.path("../", "..", "01Summaries", "oxamyl.oral.brain.RData"))
```



13544

R178924

Chemical Name: Oxamyl

PC Code: 103801
HED File Code: 13000 Tox Reviews
Memo Date: 11/3/2009
File ID: 00000000
Accession #: 000-00-0132

HED Records Reference Center
11/12/2009